Industria y Comercio

SUPERINTENDENCIA

PCT

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 03-107462

54. **TÍTULO** DERIVADOS DE AMINOQUINOLINA Y AMINOPIRIDINA Y SU USO COMO LIGANDOS Q y ADYUVANTE

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** SANOFI-SYNTHELABO

DOMICILIO París, Francia.

74. **APODERADO** EMILIO FERRERO
Código N. 1092

22. **BOGOTÁ, D. C.,** C

Industria y Comerci
SUPERINTENDENCI

PETITORIO

[illegible] Y [illegible]
Radicacion : [illegible]/462 [illegible] Folios: [illegible] 5n
Fecha ([illegible]): [illegible]-12-[illegible] [illegible]
Tramite : [illegible]
Dependencia: [illegible] DIVISION DE [illegible]

03 107462 00

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 **SOLICITUD DE:**

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

2 SOLICITANTE (71)	Nombre: **SANOFI-SYNTHELABO** sociedad constituida y existente bajo las leyes de Francia. Dirección: 174, avenue de France F-75013, Paris Francia. Domicilio: Paris, Francia.	**IDENTIFICACION** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual______ Número: ____________
3 REPRESENTANTE APODERADO	Nombre: EMILIO FERRERO Dirección: Carrera 4ª. No. 72-35 Teléfono: 347 36 11 Fax:: 217 92 11 E-mail: clientes@camyp.com. Domicilio: Bogotá, Colombia.	**IDENTIFICACION** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual______ Número: 438.019 T.P. 31.929
4 INVENTOR (ES) (72)	1 Péter ARÁNYI Bimbó út 216, H-1026 Budapest, Hungría. 2- László BALÁZS Madáchu u,15, H- 2120 Dunakeszi, Hungría. 3- Maria BALOGH Barátság u. 21, H-2120 Dunakeszi, Hungría. 4- Imre BATA Frankel Leó u. 7, H-1027 Budapest, Hungría. 5- Sándor BÁTORI Rákóczi F-268A, Rákóczi F-268/A, Hungría. 6- Lajos T. NAGY István u. 47, II/14, H-1078 Budapest, Hungría. 7- Géza TÍMÁRI Zöldfa u. 8 H-2220 Vecsés, Hunfría 8- Kinga BOÉR Vízimolnár u. 2, H-1031 Budapest, Hungría. 9- Olivier FINANCE 9, rue de Nazareth, Bat D. F-34090 Montpellier, Francia. 10- Zoltán KAPUI Etele 56/a, H-1115 Budapest, Hungría. 11-Endre MIKUS Ida u. 96, H-1162 Budapest, Hungría. 12-Zsuzsanna SZAMOSVÖLGYI Bajnok u.7, H-1063 Budapest Hungría. 13-Gábor SZELECZKY Ivánka Pál u. 30,, Hungría. 14- Katalin URBÁN-SZANÓ H-1131 Budapest, Hungría.	

5 PCT (86)
Solicitud Internacional No. PCT/HU02/00048 Fecha: 29 de mayo de 2002
Publicación Internacional No. WO 02/096879 A1 Fecha : 5 de diciembre de 2002

6 Título (54) DERIVADOS DE AMINOQUINOLINA Y AMINOPIRIDINA Y SU USO C MO LIGANDOS A3 ADENOSINA

7. **Clasificación Internacional (51)** C07D 215/48 A61K31/470

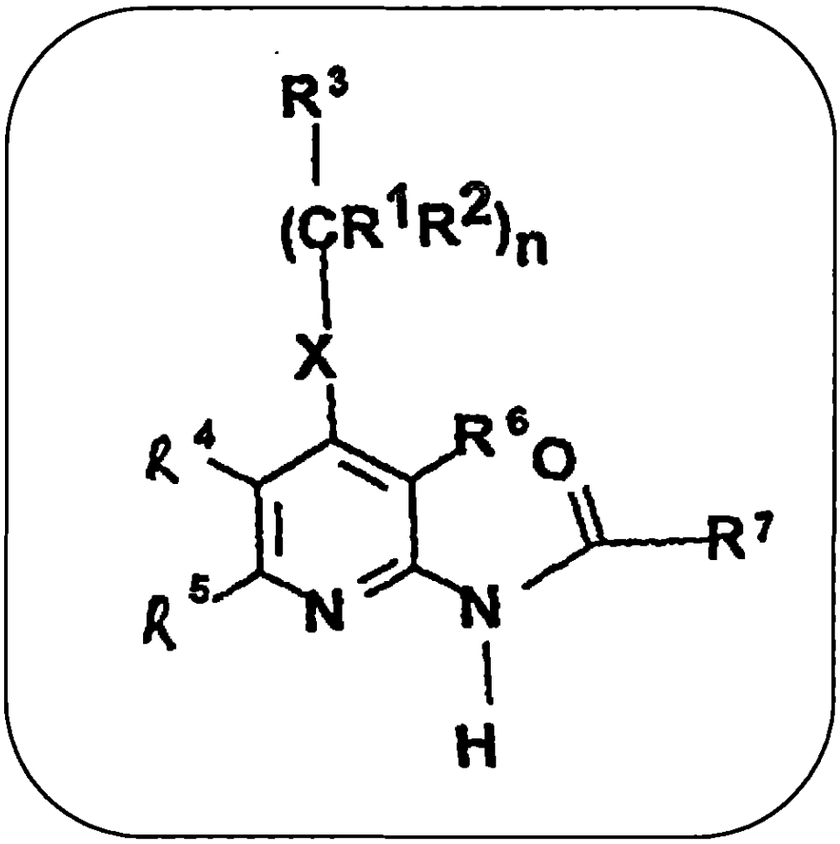
8 **Prioridad** SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	HU.	31 de mayo de 2001	P01 02279
	HU.	1 de marzo de 2002	P02 00774

9. **Comprobante de pago No.:** 03 – 85.518 **Fecha:** 24 de noviembre de 2003

10. **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por 400.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 **FIGURA CARACTERISTICA:**



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA :

C.C. 438.019 de Usaquén T.P. 31.929

PRP/mrm-Id-74-

Colombie ✓ A 4

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4ª Nº 72-35
BOGOTA, 8 - COLOMBIA

Pour brevets, modèles d'utilité, dessins industriels; marques de fabrique, de service, noms commerciaux, enseignes, slogans, licences.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica y de servicio, nombres comerciales, enseñas, lemas comerciales, licencias.

REPRESENTACION Y PODER

REPRESENTATION ET POUVOIR

10555
2260

Je (nous) soussigné (s)/Yo (nosotros), abajo firmado (s)
SANOFI-SYNTHELABO

résidant (s) à/domiciliado (s) en 174 Avenue de France,
75013 Paris, FRANCE

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª Nº 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1º del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposición, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

par cet instrument désigne (désignons) EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 et GERMAN CAVELIER, tpa. 832, domiciliés à Bogota, Colombie, Carrera 4ª Nº 72-35, conformément au paragraphe 1 de l'Article 543 du Code de Commerce, le premier comme principal et les autres comme suppléants, dans leur ordre, comme (mes) (nos) représentants dans toutes les affaires concernant la propriété industrielle ayant la faculté de recevoir les notifications et de nommer des mandataires judiciaires ou extrajudiciaires. Le premier représentant suppléant remplacera le principal en cas d'absence ou d'empêchement temporaire ou définitif de celui-ci. La même règle sera appliquée quand il faudra que le deuxième représentant suppléant remplace le premier, ou le troisième au deuxième. Dans ces cas, le représentant principal, ou le premier ou le deuxième suppléant dans leur cas, ou les deux, déclareront leur intention de ne pas exercer la représentation moyennant déclaration par devant Notaire Public en Colombie, ou par devant Notaire ou tout autre Fonctionnaire Public ou Consul de Colombie à l'étranger; et s'il s'agissait d'empêchement, avec le certificat respectif. Si l'un des nommés venait à manquer définitivement, le suivant prendrait sa place. Quand l'absence ou l'empêchement du représentant principal, ou de son premier ou second suppléant dans leur cas, aura cessé, ils pourront exercer leur représentation dans leur ordre, l'un ou les autres, suivant le cas, l'assumant par le seul fait de l'exercer, cessant à ce moment-là l'exercice de la représentation par le premier, deuxième ou troisième suppléant dans leur cas.

Par ailleurs j'(nous) octroie (octroyons) pouvoir aux avocats ci-avant mentionnés pour obtenir la protection de ma (notre) propriété industrielle et contre la concurrence déloyale; à cet effet, autorise(ons) lesdits fondés de pouvoir à me (nous) représenter devant toutes entités ou personnes, avec ou sans juridiction; notamment devant celles de l'ordre administratif, contentieux-administratif et judiciaire ainsi que devant les Tribunaux d'Arbitrage, pour tout ce qui concerne les affaires suivantes: a) l'obtention de brevets d'invention, modèles d'utilité, dessins industriels, le dépôt de marques de fabrique, collectives, défensives, de service, slogans, noms commerciaux, enseignes, variétés végétales et appellations d'origine; leur renouvellement, transfert, changement de nom ou de domicile, radiation volontaire, et l'enregistrement des contrats de licence; b) les actions de concurrence déloyale, protection du consommateur, opposition, radiation administrative ou judiciaire, annulation, contrefaçon, licences, tutelle, protection des secrets industriels, et les procès civils, pénaux, administratifs ou contentieux-administratifs ayant trait à ces droits; actions et procès établis par moi (nous) ou contre moi (nous); et c) afin que pour toutes les questions mentionnées ci-dessus, ils puissent substituer ce pouvoir, transiger, concilier, admettre les faits du procès, renoncer, et ratifier les actes des agents officieux ou personnes sans mandat.

Signé le/Dado y firmado hoy 07 JUIN 2001

à/en

Signature

Elisabeth THOURET-LEMAITRE
Directeur Brevet / Patent Director

sanofi-synthelabo
174, Avenue de France
75013 PARIS
[illegible] RCS Paris

Vu pour certification matérielle de la signature de Mme Thouret Lemaitre apposée ci-contre

12[illegible]-2004-0

LEGALIZACION

Es necesaria la legalización con certificado consular sobre la existencia legal de la compañía, que éste ejerce su objeto social y que la persona que otorga el poder está autorizada para ello. A este efecto les solicitamos que muestren al Cónsul las pruebas que acreditan estos hechos.

LEGALISATION

La légalisation consulaire est nécessaire, le Consul certifiant l'existence légale des sociétés qui octroient le pouvoir, l'exercice d'une activité conforme à leur objet social et que la personne qui octroie le pouvoir est habilitée à le faire. A cet effet il faut présenter au Consul les documents qui prouvent les faits mentionnés ci-dessus.

243/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

APOSTILLE
(Convention de La Haye du 5 Octobre 1961)

1. — **République Française**
Le présent acte public
2. — **a été signé par** ..... Mr KOENIG
3. — **agissant en qualité de** ..... Notaire
4. — **est revêtu du sceau de** ..... Notariat

ATTESTE

5. — **à Paris** ..... **le** 12 SEP. 2001
6. — **Par le Procureur Gal près la Cour d'Appel**
7. — **Sous N°** 56961
Le ..... **signature**

COUR D'APPEL DE PARIS • PROCUREUR GÉNÉRAL

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

02 DIC 2003

JUAN MANUEL BOTERO BEDOYA
NOTARIO

APOSTILLE
(Convention de La Haye du 5 Octobre 1961)

1. - **République Française**
Le présent acte public
2. - **a été signé par** .....
3. - **agissant en qualité de** .....
4. - **est revêtu du sceau de** .....

ATTESTE

5. - **à Paris** ..... **le** 12 SEP. 2001
6. - **Par le Procureur Gal près la Cour d'Appel**
7. - **Sous N°** .....
Le ..... **signature**

COUR D'APPEL DE PARIS

NOTA PARA EL SEÑOR CONSUL DE COLOMBIA: Según los artículos 65 del C. de P.C. y 480 del C. de Co., si el poderdante es una sociedad, el Señor Cónsul debe certificar que tuvo a la vista las pruebas de su existencia, que ejerce su objeto social y que quien confiere el poder es su representante.

TRADUCCIÓN OFICIAL No. 243/01 DE UN DOCUMENTO ESCRITO EN FRANCÉS, EL CUAL PARA SU IDENTIFICACIÓN SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCIÓN OFICIAL EFECTUADA EL DIA 06 DE NOVIEMBRE DEL AÑO 2001 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTÁ, TRADUCTOR OFICIAL SEGÚN RESOLUCIÓN No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

Autenticaciones que se hallan a continuación de un documento de representación y poder conferido en francés y español por **SANOFI-SYNTHELABO**, domiciliada en 174, Avenue de France, 75013, Paris, Francia y otorgado a los Doctores Emilio Ferrero TPA 31929, Gonzalo Perdomo TPA 831, Luz Clemencia de Paez TPA 23555 y Germán Cavelier TPA 832, todos domiciliados en Bogotá, Colombia, Carrera 4 No 72-35.

Dado y firmado el 07 de junio del 2001. Firma ilegible de Elizabeth THOURET-LEMAITRE (Directora patentes).

Sello: Sanofi-Synthelabo, 174, Avenue de France, 75013 Paris – 395 030 844 RCS PARIS.

Legalización de la firma de la Señora Elizabeth THOURET-LEMAITRE por el Señor Koenig, Notario en Paris. Firma ilegible del Notario.

Sello: Koenig - Notario en Paris – Tribunal Superior – República Francesa.

CONSULADO NOTARIAL SECCIÓN DE ... DE BOGOTA. HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON ... QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL ... ROTERO MEDINA
NOTARIO

APOSTILLA

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

1. - República francesa

El presente acta público

Traducción Oficial No. 243/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Autorización No. 2680/91

6

2. - Ha sido firmado por el Doctor Koenig

3. - Obrando en calidad de Notario

4. - Con sello de su Notaría

CERTIFICADO

5. - En Paris El 12 de septiembre del 2001

6. Por el Procurador General ante el Tribunal Superior

7. Bajo el número 56961/01

8. Sello: Tribunal Superior de Paris – Procurador General.

9. Firma ilegible.

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.

Traducción oficial No. 243/01

Colo: 12555-803-004-0

Traductor: Jean-Jacques Turpin.

Bogotá, D.C., 06 de noviembre del año 2001.

Traducción Oficial No. 243/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAROL
Res. Ministerio No. 2460/91

NO SE ASUME RESPONSABILIDAD DEL TEXTO
2001 NOV 13 P 12:27
JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA
02 DIC 2003
JUAN MANUEL SOTERO MEDINA
NOTARIO

MINISTERIO DE RELACIONES EXTERIORES
18940
Jean Jacques Turpin
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADO(S) CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 13 NOV. 2001

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

02 DIC 2003

JUAN MANUEL BUTERO MEDINA
NOTARIO

M4 cerfa Nº 60-01.2

déclaration présentée au CFE le :

réservé au CFE compétent

DECLARATION DE CESSATION TOTALE D'ACTIVITE ☒ / CLOTURE DE LA LIQUIDATION ☐

AVEC ☒ ou SANS ☐ DEMANDE DE RADIATION AU RCS

NUMERO(S) DE L'IMMATRICULATION PRINCIPALE

RCS 732 059 332 RCS PARIS (1973B59233)

Registre du Commerce et des Sociétés · SIREN · Répertoire des Métiers

G7550 974563 7

M GUIDABEFHJKT

Nbre d'intercalaires joints :

QUELLE QUE SOIT LA FORMALITÉ, LES RUBRIQUES SUR FOND ROUGE DOIVENT OBLIGATOIREMENT ÊTRE REMPLIES

73 B 59233

12555

DENOMINATION : SANOFI

SIGLE :

SIEGE ADRESSE y compris s'il y a lieu, l'IDENTITÉ DU DOMICILIATAIRE (Nom, Prénoms ou Dénomination) : 174 AVENUE DE FRANCE 75013 PARIS

Nº SIRET :

314486

FORME JURIDIQUE : SA

PRINCIPALES ACTIVITES DE L'ENTREPRISE : PRISE DE PARTICIPATIONS DANS TOUTES SOCIETES OU ENTREPRISES DANS LE DOMAINES DE LA SANTE

EFFECTIF SALARIE de l'entreprise : 1176

CESSATION TOTALE D'ACTIVITE de l'entreprise, indiquer la date : 18/05/1999

DISSOLUTION / DISPARITION à la suite d'une FUSION ☒ ou d'une SCISSION ☐ , indiquer la date : 18/05/1999

Personnes Morales ayant participé à l'opération (Dénomination, Forme Juridique, Adresse du siège, nº RCS) : SANOFI - SYNTHELABO 174 AVENUE DE FRANCE 75013 PARIS RCS PARIS 395 030 844

Liste à suivre sur intercalaire(s) : OUI ☐ NON ☐

PA 281555.

En cas de SUPPRESSION du SIÈGE de l'entreprise : 18/05/1999 DATE de fin d'exploitation

En cas de cessation totale d'emploi de tout salarié, préciser la date :

Préciser la DESTINATION : ☐ disparition ☐ vente ☐ apport ☐ mise en location gérance ☐ reprise par le propriétaire ☒ autre (préciser) FUSION ABSORPTION AVEC EFFET RETROACTIF AU 01-01-1999

Identité du BÉNÉFICIAIRE (Nom, Prénoms, domicile ou dénomination, adresse du siège) : SANOFI - SYNTHELABO - 174 AVENUE DE FRANCE 75013 PARIS - RCS PARIS 395 030/ 844

Lieu principal d'exploitation de l'entreprise (adresse si différente de celle du siège) :

Centre des impôts où ont été déposées les dernières déclarations de résultats et de TVA :

Le cas échéant, RÉFÉRENCES DES ÉTABLISSEMENTS (autres que le siège) SUPPRIMÉS A L'OCCASION DE CETTE DÉCLARATION :

ÉTABLISSEMENT : ADRESSE

DATE de fin d'exploitation

Nº SIRET :

En cas de cessation totale d'emploi de tout salarié, préciser la date :

Préciser la DESTINATION : ☐ disparition ☐ vente ☐ apport ☐ mise en location gérance ☐ reprise par le propriétaire ☐ autre (préciser)

Identité du BÉNÉFICIAIRE (Nom, Prénoms, domicile ou dénomination, adresse du siège) :

ÉTABLISSEMENT, ADRESSE

DATE de fin d'exploitation

Nº SIRET :

En cas de cessation totale d'emploi de tout salarié, préciser la date :

Préciser la DESTINATION : ☐ disparition ☐ vente ☐ apport ☐ mise en location gérance ☐ reprise par le propriétaire ☐ autre (préciser)

Identité du BÉNÉFICIAIRE (Nom, Prénoms, domicile ou dénomination, adresse du siège) :

ÉTABLISSEMENT : ADRESSE

DATE de fin d'exploitation

Nº SIRET :

En cas de cessation totale d'emploi de tout salarié, préciser la date :

Préciser la DESTINATION : ☐ disparition ☐ vente ☐ apport ☐ mise en location gérance ☐ reprise par le propriétaire ☐ autre (préciser)

Identité du BÉNÉFICIAIRE (Nom, Prénoms, domicile ou dénomination, adresse du siège) :

Liste à suivre sur intercalaire(s) : OUI ☐ NON ☐

MINISTERE DE L'INDUSTRIE · INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE · MINISTERE DE L'ECONOMIE DES FINANCES

(Convention de La Haye du 5 Octobre 1961)

République Française

Le présent acte public

2. - a été signé par ...

3. - agissant en qualité de ...

4. - est revêtu du sceau de L'INPI

ATTESTE

Paris le 12 SEP. 2001

Par le Procureur Gal près la Cour d'Appel

Nº 563...

NOTARIO SEXTO DEL CIRCULO DE BOGOTA; HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL

02 OCT 2003

PROCUREUR

JUAN MANUEL BOTERO ME...

NOTARIO

Traducteur Officiel No. 245/01

JEAN - JACQUES H. TURPIN

Traducteur Intérprete Oficial

FRANCÉS - ESPAÑOL

Res. Ministerio No. 2480/91

ADRESSE PERMANENTE pour la correspondance : 174 AVENUE DE FRANCE 75013 PARIS

tél. :

LE SOUSSIGNÉ : LES PETITES AFFICHES (LM) 2, RUE MONTESQUIEU 75001 PARIS

09/0909.254

demande que ce document constitue demande d'INSCRIPTION MODIFICATIVE au RCS ☒, au RM ☐, au RSAC ☐, au REBA ☐, de RADIATION au RCS ☐, au RM ☐, au RSAC ☐, au REBA ☐, et déclaration aux Services Fiscaux, aux Organismes de Sécurité Sociale, à l'INSEE, et s'il y a lieu, à l'Inspection du Travail et à l'ASSEDIC

Fait à ... le ... signature

La loi nº 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés, s'applique aux réponses faites à ce formulaire par les personnes physiques. Elle leur garantit un droit d'accès et de rectification pour les données les concernant auprès des organismes destinataires de ce formulaire. Les déclarations inexactes peuvent, dans certains cas, exposer leurs auteurs à des sanctions pénales.

Mod. 840 012 Berger Levrault Nancy (A)

CHAMBRE DE MÉTIERS

DE :

NUMÉRO D'IMMATRICULATION RM :

NOM OU DÉNOMINATION :

RÉPERTOIRE DES MÉTIERS

SIGLE

☐ DEMANDE D'IMMATRICULATION ☐ INSCRIPTION DE MENTION DE CONJOINT COLLABORATEUR (Personnes Physiques uniquement)	☐ DÉCLARATION DE MODIFICATION	☐ DEMANDE DE RADIATION ☐ RADIATION DE MENTION DE CONJOINT COLLABORATEUR (Personnes Physiques uniquement)

STAGE D'INITIATION À LA GESTION (article 2 de la loi du 23.12.82)	en cas de DÉCISION du PRÉSIDENT de la CHAMBRE DE MÉTIERS (article 11 du décret du 10.06.83)	(articles 12 et 13 du décret du 10.06.83)
Attestation - date de délivrance :	Date du dépôt de la demande :	Date de la transmission à la Commission de Qualification :
Dispense - motif de la dispense :	Demande de renseignements complémentaires :	Date de la notification :
		Paiement de la redevance : en F
PIÈCES JUSTIFICATIVES :	Production des renseignements demandés :	☐ espèces ☐ chèque bancaire ☐ chèque postal
	Date limite de la décision du Président :	Référence du Registre à souches :
	DÉCISION DU PRÉSIDENT :	Affichage du : ☐ NON ☐ OUI
	P.V. n° en date du : ☐ Accord ☐ Rejet	

La conformité des déclarations ci-annexées avec les pièces justificatives produites a été vérifiée sous notre responsabilité

DATE DE L'INSCRIPTION,

Le Président de la Chambre de Métiers

CADRE RÉSERVÉ À L'INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

MINISTÈRE DE L'ÉCONOMIE

POUR LE DIRECTEUR GÉNÉRAL DE L'INPI

LE CHEF DE DÉPARTEMENT

18 JUIN 1999

JUAN MANUEL SOBRINO MEDINA

NOTARIO

NOTA : Les Greffiers et l'Institut National de la Propriété Industrielle sont autorisés et seuls habilités à délivrer à toute personne qui en fait la demande des certificats, copies ou extraits des inscriptions portées au registre et actes déposés en annexe, sauf en ce qui concerne les inscriptions radiées, qui sont communiquées dans les conditions prévues (article 68 du décret n° 84-406 du 30 mai 1984, art. 87)

IMMATRICULATION ☐ PRINCIPALE ☐ SECONDAIRE — INSCRIPTION ☐ COMPLÉMENTAIRE ☐ MODIFICATIVE — ☐ CORRECTION ☐ RADIATION

REGISTRE DU COMMERCE ET DES SOCIÉTÉS

GREFFE DU TRIBUNAL

DE :

CODE GREFFE :

8

TRADUCCIÓN OFICIAL No. 245/01 DE UN DOCUMENTO ESCRITO EN FRANCÉS, EL CUAL PARA SU IDENTIFICACIÓN SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCIÓN OFICIAL EFECTUADA EL DIA 06 DE NOVIEMBRE DEL AÑO 2001 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTÁ, TRADUCTOR OFICIAL SEGÚN RESOLUCIÓN No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

SECRETARIADO DEL TRIBUNAL DE PARIS

Código del Secretariado: 7501

Número de referencia : (en blanco)

Número de matrícula RCS : 73 B 5933

Nombre o denominación : (en blanco)

Sigla : (en blanco)

Espacio reservado para el secretariado del Tribunal: *(en blanco)*

REGISTRO DEL COMERCIO Y SOCIEDADES

Matrícula:	Principal	_____	segundaria	_____
Inscripción	Complementaria	_____	modificativa	_____
Corrección		_____	**Cancelación**	X

Fecha de radicación en el Secretariado del Tribunal : (en blanco)

Número de radicación en el Secretariado del Tribunal : (en blanco)

NOTA: Los Secretarios de los Tribunales y el Instituto de la Propiedad Industrial están obligados, y son los únicos habilitados, a expedir a cualquier persona que lo solicite certificaciones, copias o certificados de las inscripciones llevadas en el registro y actas depositados en anexo, salvo lo relacionado con las inscripciones canceladas, las cuales se comunican de acuerdo con las condiciones establecidas por la resolución (del 24 de Septiembre de 1984), prevista en el artículo 88 (decreto No. 84-[illegible]6 del 30 de mayo de 1984, art.67)

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUERON A LA VISTA
02 DIC 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO

Traducción Oficial No. 245/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Ministerio No. 2680/91

DOCUMENTOS DE PRUEBA : (en blanco)

ACTIVIDADES REGLAMENTADAS (doc. No. 24) : (en blanco)

FECHA de PRESENTACIÓN de los ESTATUTOS : (en blanco)

OBSERVACIONES del SECRETARIO DEL TRIBUNAL : (en blanco)

Sello: Tribunal de Comercio de Paris con fecha del 16 de junio de 1999, No. de radicación 118.

La conformidad de las declaraciones adjuntas con los documentos justificativos presentados en aplicación de los reglamentos ha sido verificada por el suscrito Secretario del Tribunal quien luego procedió a la inscripción antes señalada.

FECHA DE LA INSCRIPCIÓN : (en blanco)

Certificado por el Secretario del Tribunal : (en blanco)

Espacio reservado para el **Registro Nacional del Comercio y Sociedades**: (en blanco).

CÁMARA OFICIAL DE ARTESANOS DE: (en blanco)

Espacio reservado para la Cámara Oficial de Artesanos

NÚMERO DE GESTIÓN : (en blanco)

NÚMERO DE MATRÍCULA RM : (en blanco)

NOMBRE O DENOMINACIÓN : (en blanco)

Siren : (en blanco)

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

02 DIC 2003

JUAN MANUEL GUTIERREZ GALINA NOTARIO

245/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Ministerio No. 2480/91

10

REPERTORIO DE LAS PROFESIONES

_____ SOLICITUD DE MATRICULA

_____ INSCRIPCIÓN DE MENCIÓN DE CÓNYUGE COLABORADOR (únicamente para personas naturales)

_____ DECLARACIÓN DE MODIFICACIÓN

_____ SOLICITUD DE CANCELACIÓN

_____ CANCELACIÓN DE MENCIÓN DE CÓNYUGE COLABORADOR (únicamente para personas naturales)

CURSO DE INICIACIÓN A LA GESTIÓN (artículo 2 de la ley del 23/12/82)

Certificación - fecha de expedición : (en blanco)

Dispensa - motivo de la dispensa : (en blanco)

DOCUMENTOS DE PRUEBA : (en blanco)

en caso de DECISIÓN del PRESIDENTE de la CÁMARA OFICIAL DE ARTESANOS

(artículo 11 del Decreto del 10/06/83)

Fecha de presentación de la solicitud : (en blanco)

Solicitud de informaciones adicionales : (en blanco)

Presentación de las informaciones solicitadas : (en blanco)

Fecha límite de la decisión del Presidente : (en blanco)

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

02 DIC 2003

MANUEL BOTERO MEDINA
NOTARIO

245/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

DECISIÓN DEL PRESIDENTE:

Acta No.: (en blanco), con fecha del (en blanco)

_____ Acordado _____ Negado

en caso de PRESENTACIÓN en COMISIÓN del REPERTORIO DE LAS PROFESIONES (artículos 12 y 13 del Decreto del 10/06/83)

Fecha de transmisión a la Comisión de Repertorio : (en blanco)

Fecha de la notificación : (en blanco)

Pago del impuesto : (en blanco) en F.

_____ efectivo _____ cheque bancario _____ cheque postal

Referencia del Registro con talonario : (en blanco)

Fijación en cartelera: del (en blanco) al (en blanco)

Se verificó bajo nuestra responsabilidad la conformidad de las declaraciones adjuntas con base en los documentos justificativos presentados en aplicación de los reglamentos.

FECHA DE LA INSCRIPCIÓN : (en blanco)

El Presidente de la Cámara Oficial de Artesanos : (en blanco)

NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR: QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003

Espacio reservado al Instituto Nacional de la Propiedad Industrial: (en blanco)

245/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

Declaración presentada en el CFE el: (en blanco)

DECLARACIÓN DE **CESACIÓN TOTAL DE ACTIVIDAD** ____

CIERRE DE LA LIQUIDACIÓN ____

CON __X__ **o** **SIN** ____ **SOLICITUD DE CANCELACIÓN EN EL RCS**

NÚMERO(S) DE LA MATRÍCULA PRINCIPAL

RCS 732 059 332 R.C.S. PARIS (1973B5933)

73 B 5933

PERSONA JURÍDICA: G7550 974563 7

M G U I D A B E F H J K T

Nº de páginas adicionales adjuntas: (en blanco)

DENOMINACIÓN: SANOFI **SIGLA :** (en blanco)

SEDE: DIRECCIÓN incluyendo si hay lugar LA IDENTIDAD DEL DOMICILIARIO:

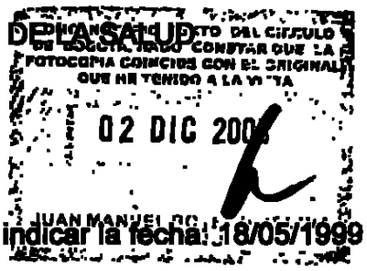
174, AVENUE DE FRANCE 75013 PARIS

Nº SIRET: (en blanco)

FORMA JURÍDICA: SA

PRINCIPALES ACTIVIDADES DE LA EMPRESA: TOMA DE PARTICIPACIONES EN CUALQUIER SOCIEDAD O EMPRESA EN EL CAMPO DE LA INDUSTRIA

NÚMERO DE ASALARIADOS: 1176



CESACIÓN TOTAL DE LA ACTIVIDAD de la empresa, indicar la fecha: 18/05/1999

DISOLUCIÓN / DESAPARICIÓN a consecuencia de una FUSIÓN __X__ o ESCISIÓN

_____ , indicar la fecha: 18/05/1999

Traducción Oficial No. 245/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Ministerio No. 2680/91

Personas jurídicas que participaron en la operación (Denominación, forma jurídica, dirección de la sede, nº RCS):

SANOFI – SYNTHELABO - 174, AVENUE DE FRANCE, 75013 PARIS

RCS PARIS 395 030 844

PA 2815199

En caso de SUPRESIÓN de la SEDE de la empresa: (en blanco)

En caso de cesación total de empleo de cualquier asalariado, indicar la fecha: (en blanco)

FECHA de fin de explotación: 18/05/1999

Indicar el DESTINO:

_____ Desaparición **_____ venta** **_____ aportación**

_____ puesta en alquiler gerencia **_____ retoma por parte del propietario**

__X__ Otros (precisar)

FUSIÓN ABSORCIÓN CON EFECTO RETROACTIVO AL 01/01/1999

Identidad del BENEFICIARIO: SANOFI – SYNTHELABO - 174 AVENUE DE FRANCE 75013 PARIS – RCS PARIS 395 030 844

NOTARIA DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
MANUEL ROJERO MEDINA
NOTARIO

Lugar principal de explotación de la empresa: (en blanco)

Oficina de recaudo de impuestos donde se presentaron las últimas declaraciones de resultados y del IVA: (en blanco)

245/01
Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

Si es el caso, REFERENCIAS DE LOS ESTABLECIMIENTOS (diferentes a la sede) SUPRIMIDOS CON OCASIÓN DE ESTA DECLARACIÓN:

ESTABLECIMIENTO: DIRECCIÓN: (en blanco)

Nº de SIRET: (en blanco)

En caso de cesación total de empleo de cualquier asalariado, indicar la fecha: (en blanco)

Indicar el DESTINO:

_____ Desaparición _____ venta _____ aportación

_____ puesta en alquiler gerencia _____ retoma por parte del propietario

_____ Otros (precisar)

Identidad del BENEFICIARIO: (en blanco)

DIRECCIÓN PERMANENTE para la correspondencia: 174, AVENUE DE FRANCE 75013 PARIS

EL SUSCRITO "LES PETITES AFFICHES" (LM) 2, RUE MONTESQUIEU, 75001 PARIS solicita que el presente documento constituya una solicitud de INSCRIPCIÓN:

- **MODIFICATIVA** en el RCS ___X___ , en el RM _____ en el RSAC _____ en el REBA_____ ,

- de **CANCELACIÓN** en el RCS _____ RM _____ RSAC _____ REBA _____

y una declaración a los Servicios Fiscales, Organismos del Seguro Social, INSEE y si es o deja de ser EMPLEADOR, en la Inspección del Trabajo y en el ASSEDIC.

Dado en (ilegible), el (ilegible). Firma ilegible.

COMO NOTARIO ACEPTO DEL INTERESADO
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO

245/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Ministerio No. 2680/91

Sello: Copia certificada en el RNCS de Lille, con fecha del 31/07/01. Por el Director General del INPI, firma ilegible del Jefe de Departamento.

Sello: Instituto Nacional de la Propiedad Industrial - República Francesa.

Sello: Ministerio de Economía, Hacienda e Industria - Instituto Nacional de la Propiedad Industrial – República Francesa.

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)

1. República Francesa

   El presente acta público

2. Ha sido firmado por el funcionario encargado

3. Actuando en calidad funcionario encargado

4. Con sello del INPI

Certificado

5. En Paris 6. El 12 de septiembre del 2001

7. Por el Procurador General ante el Tribunal Superior

8. Bajo el número 56831/01

9. Sello / estampilla: Tribunal Superior de Paris – Fiscalía - República Francesa.

10. Firma ilegible.

MINISTERIO DE RELACIONES EXTERIORES
VERIFICACIÓN DE LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
1 8 9 4 1 1
NO SE ASUME RESPONSABILIDAD DEL TEXTO
2001 NOV 13 P 12:
JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.
COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL SOTER MEDINA

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.
Traducción oficial No. 245/01
COLO: 12555-803-004-0
Traductor: Jean-Jacques Turpin.
Bogotá, D.C., 06 de noviembre del 2001

245/01
Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2480/91

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADOS CON C.C. No.(s)

PERSONA(S) AUTENTICADA(S) EN BOGOTA. 13 NOV. 2001

NOTARIO SEXTO DE SANTAFE DE BOGOTA

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

02 DIC 2003

JUAN MANUEL ESTEVEZ MEDINA
NOTARIO

16 a

12555

GREFFE DU TRIBUNAL

DE : Paris

CODE GREFFE : 501

B 393 393

REGISTRE DU COMMERCE ET DES SOCIÉTÉS

IMMATRICULATION	☐ PRINCIPALE ☐ SECONDAIRE	INSCRIPTION	☐ COMPLÉMENTAIRE ☒ MODIFICATIVE	☐ CORRECTION ☐ RADIATION

Date d'arrivée au Greffe :

Numéro d'arrivée au Greffe :

NOTA : Les Greffiers et l'Institut National de la Propriété Industrielle sont astreints et seuls habilités à délivrer à toute personne qui en fait la demande des certificats, copies ou extraits des inscriptions portées au registre et actes déposés en annexe, sauf en ce qui concerne les inscriptions radiées, qui sont communiquées dans les conditions fixées par l'arrêté *(du 24 septembre 1984)*, prévu à l'article 88 (décret n° 84-406 du 30 mai 1984, art. 67)

PIÈCES JUSTIFICATIVES :

ACTIVITÉS RÉGLEMENTÉES (pièce n° 24) :

DATE de DÉPÔT des STATUTS : 24 SEP. 1996

OBSERVATIONS du GREFFIER :

Numéro de référence :

SIGLE :

NUMÉRO D'IMMATRICULATION RCS :

NOM OU DÉNOMINATION :

La conformité des déclarations ci-annexées avec les pièces justificatives produites en application des règlements a été vérifiée par le Greffier soussigné qui a procédé en conséquence à l'inscription ci-dessus désignée

DATE DE L'INSCRIPTION :

Certifié, le Greffier

TRIBUNAL DE PARIS

CADRE RÉSERVÉ AU REGISTRE NATIONAL DU COMMERCE ET DES SOCIÉTÉS

MINISTÈRE DE L'ÉCONOMIE DES FINANCES ET DE L'INDUSTRIE

INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

9/10/01

CADRE RÉSERVÉ A L'INSTITUT NATIONAL DE LA PROPRIÉTÉ INDUSTRIELLE

La conformité des déclarations ci-annexées aux pièces justificatives produites en application des règlements a été vérifiée par nos mandataires

DATE DE L'INSCRIPTION,

Le Président de la Chambre de Métiers :

STADE D'IMMATRICULATION A LA GESTION
(article 2 de la loi du 23/12/82)

Absorption - date de clôture :

Dépense - motif de la dépense :

PIÈCES JUSTIFICATIVES :

Fondation des renseignements demandés :

☐ espèces ☐ chèque bancaire ☐ chèque postal

Référence du Registre à souches :

Affichage du

au

en cas de DÉCISION du PRÉSIDENT de la CHAMBRE DE MÉTIERS
(article 11 du décret du 10.8.83)

Date dépôt de la demande :

Demande de renseignements complémentaires :

Date limite de la décision du Président :

DÉCISION DU PRÉSIDENT :

en date du :

☐ Accord ☐ Refus

en cas de MISSIVE en COMMISSION de RÉFÉRENDUM DES MÉTIERS
(articles 12 et 13 du décret du 10.8.83)

Date de la transmission à la Commission de Référence :

Date de notification :

Référence de la demande : en F

Référence du Registre à souches :

Affichage du

au

☐ DEMANDE D'IMMATRICULATION
☐ INSCRIPTION DE MENTION DE CONJOINT COLLABORATEUR Personne Physique uniquement

☐ DÉCLARATION DE MODIFICATION

☐ DEMANDE DE RADIATION
☐ RADIATION DE MENTION DE CONJOINT COLLABORATEUR Personne Physique concernée

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RÉPERTOIRE DES MÉTIERS

CHAMBRE DE MÉTIERS

DE :

NUMÉRO D'IMMATRICULATION RM : RM

NOM OU DÉNOMINATION :

0075 I

Numéro de gestion :

Liasse MC

M2 cerfa
N° 98-0165
déclaration présentée au CFE le

réservé au CFE compétent

La Liasse doit être adressée dans son intégralité au CFE, elle est indissociable sauf cas particulier prévu par le décret n° 81-257 du 18/03/81 (à voir avec le CFE)

DECLARATION DE MODIFICATION

de L'ENTREPRISE — IDENTIFICATION ☐ — CARACTÉRISTIQUES ☐ — DIRIGEANTS ☐ — TRANSFERT du SIÈGE ☒ — DISSOLUTION ☐

de L'ETABLISSEMENT — OUVERTURE ☐ — IDENTIFICATION ☐ (Y COMPRIS TRANSFERT) — DIRIGEANTS ☐ — ACTIVITÉS ☐ — FERMETURE ☐

Autres modifications (à préciser s'il y a lieu)

Décret n° 81-257 du 18 mars 1981 modifié créant des Centres de Formalités des Entreprises

NUMERO(S) DE L'IMMATRICULATION PRINCIPALE

732 059 332 RCS PARIS — RM — 73 B 5938

G7550 9397 5 2

M G U I D A B E F H J K T

QUELLE QUE SOIT LA FORMALITÉ, LES RUBRIQUES SUR FOND ROUGE DOIVENT OBLIGATOIREMENT ÊTRE REMPLIES
ET SI LA MODIFICATION CONCERNE UN ÉTABLISSEMENT LES RUBRIQUES SUR FOND NOIR DOIVENT AUSSI ÊTRE REMPLIES

56506

IDENTIFICATION / et le cas échéant NOUVELLE IDENTIFICATION au

DÉNOMINATION SANOFI

SIGLE

IDENTIFICATION ANCIENNE en cas de modification

DÉNOMINATION

SIGLE

SIEGE (ou en cas de transfert, nouveau siège) ADRESSE y compris s'il y a lieu, l'IDENTITÉ DU DOMICILIATAIRE (Nom, Prénoms ou Dénomination) 174 AVENUE DE FRANCE 75013 PARIS

N° SIRET

FORME JURIDIQUE SOCIETE ANONYME

PRINCIPALES ACTIVITES DE L'ENTREPRISE PRISE DE PARTICIPATIONS DANS TOUTES SOCIETES OU ENTREPRISES DANS LE DOMAINES DE LA SANTE ET DE LA CHIMIE ETC

EFFECTIF SALARIÉ de l'entreprise 1244

NOM COMMERCIAL

CAPITAL montant 2 659 121 675 FRS ou si société à capital variable, montant minimum

DURÉE de la personne Morale ans en cas de société soumise à publicité annuelle de ses comptes, DATE DE CLOTURE de l'exercice social

DIRIGEANTS et le cas échéant, ADMINISTRATEURS COMMISSAIRES AUX COMPTES et ASSOCIÉS tenus indéfiniment et solidairement des dettes sociales, MEMBRES du GIE, LIQUIDATEURS. Pour l'établissement décrit ci-dessous s'il y a lieu, Personne(s) ayant le pouvoir d'engager par sa (leur) signature la responsabilité de l'entreprise (FONDÉ(S) DE POUVOIR) PROPRIÉTAIRES INDIVIS DU FONDS.

ou NOM Prénoms DÉNOMINATION
ou DOMICILE ADRESSE DU SIEGE
qualité ancienne (s'il y a lieu) — qualité actuelle ou nouvelle — date de naissance — dépt.

ou NOM Prénoms DÉNOMINATION
ou DOMICILE ADRESSE DU SIEGE
qualité ancienne (s'il y a lieu) — qualité actuelle ou nouvelle — date de naissance — dépt.

ou NOM Prénoms DÉNOMINATION
ou DOMICILE ADRESSE DU SIEGE
qualité ancienne (s'il y a lieu) — qualité actuelle ou nouvelle — date de naissance — dépt.

Tal de COMMERCE de PARIS
N° dépôt 51141
24 SEP 1998

Liste à suivre sur intercalaire(s) OUI ☐ NON ☐

En cas de DISSOLUTION la Société poursuit son exploitation pour les besoins de la liquidation OUI ☐ NON ☐ préciser dans le cadre DIRIGEANTS les références du (ou des) LIQUIDATEUR(S)
Indiquer le titre et la date du journal d'annonces légales ayant publié la nomination du (ou des) liquidateur(s)

En cas de TRANSFERT du SIEGE dans le ressort d'un autre Tribunal, indiquer les GREFFES où sont éventuellement souscrites les immatriculations secondaires

Liste à suivre sur intercalaire(s) OUI ☐ NON ☐

En cas de MODIFICATION du CAPITAL à la suite d'une FUSION ☐ ou d'une SCISSION ☐, Personnes Morales ayant participé à l'opération (Dénomination Forme Juridique Adresse du siège n° RCS)

Liste à suivre sur intercalaire(s) OUI ☐ NON ☐

Si LA FORMALITÉ CONCERNE UN ÉTABLISSEMENT - LES RUBRIQUES SUR FOND NOIR DOIVENT ÊTRE OBLIGATOIREMENT REMPLIES

ÉTABLISSEMENT CONCERNÉ et le cas échéant **NOUVELLE IDENTIFICATION** au 01/09/1998

ADRESSE si différente du siège (PRINCIPAL ÉTABLISSEMENT s'il se confond avec le siège) en cas de transfert, nouvelle adresse

174 AVENUE DE FRANCE 75013 PARIS

N° SIRET

Cet établissement est (pour l'entreprise) nouveau ☒ modifié ☐ supprimé ☐

CATÉGORIE(S) siège ☒ établissement principal ☒ établissement secondaire ☐

ENSEIGNE

ANCIEN ÉTABLISSEMENT en cas de transfert

ANCIEN LIBELLÉ DE L'ADRESSE si changement par décision du conseil municipal

ADRESSE

32/34 RUE MARBEUF 75008 PARIS

En cas de TRANSFERT du SIÈGE ou de l'ÉTABLISSEMENT N° SIRET

Si cessation d'emploi de tout salarié, date Maintien d'une activité à l'ancien siège OUI ☐ NON ☒

ANALYSE DE LA MODIFICATION INTERVENUE

En cas d'OUVERTURE de l'établissement, de MODIFICATION DU MODE D'EXPLOITATION, d'ADJONCTION D'ACTIVITÉ, préciser 01/09/1998 ORIGINE

☒ création ☐ transfert d'activité ☐ achat ☐ apport ☐ reprise après loc. gérance ☐ prise en location gérance ☐ autre (préciser)

En cas de FERMETURE de l'établissement, de MODIFICATION DU MODE D'EXPLOITATION, de SUPPRESSION D'ACTIVITÉ, préciser ~~01/09/1998~~ DESTINATION

☒ disparition ☐ transfert d'activité ☐ vente ☐ apport ☐ reprise par le propriétaire ☐ mise en location gérance ☐ autre (préciser)

Identité du PRÉCÉDENT EXPLOITANT nom, prénoms, adresse ou dénomination

n° RCS ou SIREN

S'il y a lieu date de radiation ou de modification au RCS du précédent exploitant

En cas d'ACQUISITION du FONDS (par ACHAT ou APPORT) indiquer le titre et la date du journal d'annonces légales ayant publié la cession

Identité du BÉNÉFICIAIRE nom, prénoms, adresse ou dénomination, adresse du siège

En cas de PRISE EN LOCATION-GÉRANCE, indiquer la durée du contrat du au et s'il est renouvelable par tacite reconduction OUI ☐ NON ☐

Identité du LOUEUR du FONDS nom, prénoms, adresse ou dénomination, adresse du siège

ACTIVITÉS EXERCÉES dans cet établissement au jour de la formalité permanentes ☐ saisonnières ☐ ambulant ☐ / suite à ☐ ☐ ☐ d'exploitation

ACTIVITÉ PRINCIPALE

ACTIVITÉS SECONDAIRES

Observations éventuelles du déclarant ou autre(s) modification(s) DATE de la modification

ADRESSE PERMANENTE 174 AVENUE DE FRANCE 75013 PARIS

LE SOUSSIGNÉ LES PETITES AFFICHES (ML) 2, RUE MONTESQUIEU 75001 PARIS 09/N912 484

nom patronymique, nom d'usage, prénoms, en cas de mandataire, préciser dénomination sous laquelle il exploite

Mandataire

demande d'INSCRIPTION au RCS ☒ au RM ☐, au RSAC ☐ au REBA ☐ de RADIATION au RCS ☐ au RM ☐ au RSAC ☐ au REBA ☐

et déclaration aux Services Fiscaux, aux Organismes de Sécurité Sociale à l'INSEE, et s'il est ou cesse d'être EMPLOYEUR, à l'Inspection du Travail et à l'ASSEDIC

demande que ce document constitue

23/09/97

02 DEC 1997

Loi n° 78-17 du 6 janvier 1978 relative à l'informatique, aux fichiers et aux libertés. Art. 27 : les informations demandées sont nécessaires à l'enregistrement de la déclaration et sont destinées aux seuls services habilités de l'organisme destinataire. Elles font l'objet d'un traitement informatisé. Art. 34 : les personnes physiques ont un droit d'accès et de rectification aux informations qui les concernent. Art. 36 : sauf opposition de leur part, ces informations peuvent être cédées à des tiers.

AP[illegible]

(Convention de La[illegible] 5 Octobre 1961)

1. - République Fra[illegible]

Le présent acte p[illegible]

2. - a été signé par [illegible]

3. - agissant en qualité de [illegible]

4. - est revêtu du sceau de [illegible]

ATTESTE

5. A Paris, le [illegible]

[illegible] de la Cour d'App[illegible]

[illegible]

signature

[illegible]

Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

02 DIC 2003

CORO NOTARIAL
DE BOGOTA, HACE CONSTAR QUE LA
FOTOCOPIA CORRESPONDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA

JUAN MANUEL [illegible]
NOTARIO

TRADUCCIÓN OFICIAL No. 244/01 DE UN DOCUMENTO ESCRITO EN FRANCÉS, EL CUAL PARA SU IDENTIFICACIÓN SE SELLA CON EL SELLO DEL TRADUCTOR. ESTA ES UNA TRADUCCIÓN OFICIAL EFECTUADA EL DIA 06 DE NOVIEMBRE DEL AÑO 2001 POR JEAN-JACQUES TURPIN, C.E.: 193849 DE BOGOTÁ, TRADUCTOR OFICIAL SEGÚN RESOLUCIÓN No. 2680/91 DEL 19 DE DICIEMBRE DE 1991, EXPEDIDA POR EL MINISTERIO DE JUSTICIA DE COLOMBIA.

SECRETARIADO DEL TRIBUNAL DE PARIS

Código del Secretariado: 7501

Número de referencia : (en blanco)

Número de matrícula RCS : (en blanco)

Nombre o denominación : (en blanco)

Sigla : (en blanco)

Espacio reservado para el secretariado del Tribunal: *73 B 5933*

REGISTRO DEL COMERCIO Y SOCIEDADES

Matrícula:	Principal	_____	segundaria	_____
Inscripción	Complementaria	_____	modificativa	X
Corrección		_____	**Cancelación**	_____

Fecha de radicación en el Secretariado del Tribunal : (en blanco)

Número de radicación en el Secretariado del Tribunal : (en blanco)

NOTA: Los Secretarios de los Tribunales y el Instituto de la Propiedad Industrial están obligados, y son los únicos habilitados, a expedir a cualquier persona que lo solicite certificaciones, copias o certificados de las inscripciones llevadas en el registro y actas depositados en anexo, salvo lo relacionado con las inscripciones canceladas, las cuales se comunican de acuerdo con las condiciones establecidas por la resolución (del 24 de Septiembre de 1984), prevista en el artículo 88 (decreto No. 84-406 del 30 de mayo de 1984, art.67)

02 DIC 2003

JUAN MANUEL PEÑA MEDINA
NOTARIO

244/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

DOCUMENTOS DE PRUEBA : ilegible

ACTIVIDADES REGLAMENTADAS (doc. No. 24) : (en blanco)

FECHA de PRESENTACIÓN de los ESTATUTOS : 24 de septiembre de 1996

OBSERVACIONES del SECRETARIO DEL TRIBUNAL : (en blanco)

La conformidad de las declaraciones adjuntas con los documentos justificativos presentados en aplicación de los reglamentos ha sido verificada por el suscrito Secretario del Tribunal quien luego procedió a la inscripción antes señalada.

FECHA DE LA INSCRIPCIÓN : (en blanco)

Certificado por el Secretario del Tribunal : Firma ilegible

Sello: Tribunal de Comercio de Paris – República Francesa. 24 de septiembre de 1998.

Espacio reservado para el **Registro Nacional del Comercio y Sociedades**: (en blanco).

CÁMARA OFICIAL DE ARTESANOS DE: (en blanco)

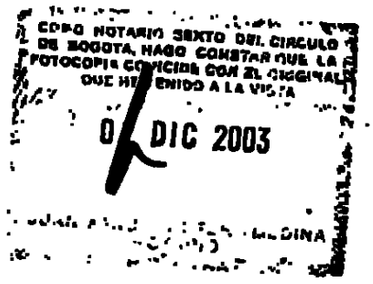
Espacio reservado para la Cámara Oficial de Artesanos.

NÚMERO DE GESTIÓN : (en blanco)

NÚMERO DE MATRÍCULA RM : (en blanco)

NOMBRE O DENOMINACIÓN : (en blanco)

Siren : (en blanco)



Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2480/91

REPERTORIO DE LAS PROFESIONES

_____ SOLICITUD DE MATRICULA

_____ INSCRIPCIÓN DE MENCIÓN DE CÓNYUGE COLABORADOR (únicamente para personas naturales)

_____ DECLARACIÓN DE MODIFICACIÓN

_____ SOLICITUD DE CANCELACIÓN

_____ CANCELACIÓN DE MENCIÓN DE CÓNYUGE COLABORADOR (únicamente para personas naturales)

CURSO DE INICIACIÓN A LA GESTIÓN (artículo 2 de la ley del 23/12/82)

Certificación - fecha de expedición : (en blanco)

Dispensa - motivo de la dispensa : (en blanco)

DOCUMENTOS DE PRUEBA : (en blanco)

en caso de DECISIÓN del PRESIDENTE de la CÁMARA OFICIAL DE ARTESANOS (artículo 11 del Decreto del 10/06/83)

Fecha de presentación de la solicitud : (en blanco)

Solicitud de informaciones adicionales : (en blanco)

Presentación de las informaciones solicitadas : (en blanco)

Fecha límite de la decisión del Presidente : (en blanco)

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

02 DIC 2003

JUAN MANUEL BUTERO MEDINA
NOTARIO

Traducción Oficial No. 244/01
JEAN - JACQUES M. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

DECISIÓN DEL PRESIDENTE:

Acta No.: (en blanco), con fecha del (en blanco)

_____ Acordado _____ Negado

en caso de PRESENTACIÓN en COMISIÓN del REPERTORIO DE LAS PROFESIONES (artículos 12 y 13 del Decreto del 10/06/83)

Fecha de transmisión a la Comisión de Repertorio : (en blanco)

Fecha de la notificación : (en blanco)

Pago del impuesto : (en blanco) en F.

_____ efectivo _____ cheque bancario _____ cheque postal

Referencia del Registro con talonario : (en blanco)

Fijación en cartelera: del (en blanco) al (en blanco)

Se verificó bajo nuestra responsabilidad la conformidad de las declaraciones adjuntas con base en los documentos justificativos presentados en aplicación de los reglamentos.

FECHA DE LA INSCRIPCIÓN : (en blanco)

El Presidente de la Cámara Oficial de Artesanos : (en blanco)

Espacio reservado al Instituto Nacional de la Propiedad Industrial: (en blanco)

CURO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA
02 DIC 2003
JUAN MANUEL SOTERO MEDINA
NOTARIO

244/01

Traducción Oficial No.
JEAN - JACQUES H. TUPPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2480/91

Declaración radicada en el CFE el (en blanco)

DECLARACIÓN DE MODIFICACIÓN

de la COMPAÑÍA:

IDENTIFICACIÓN	_____	CARACTERÍSTICAS	_____
DIRIGENTES	_____	TRASLADO DE SEDE	X
DISOLUCIÓN	_____		

del ESTABLECIMIENTO:

APERTURA	_____	IDENTIFICACIÓN	_____
DIRIGENTES	_____	ACTIVIDADES	_____
CIERRE	_____		

Otras modificaciones (precisar si hay lugar): (en blanco)

NÚMERO(S) DE LA MATRÍCULA PRINCIPAL: 732 059 332 R.C.S. PARIS

RM: 73 B 5933

PERSONA JURÍDICA: G7550 939765 2

M G U I D A B E F H J K T

Doc. Sociales adjuntos: (en blanco) Páginas adicionales adjuntas: (en blanco)

COBO NOTARIO SEXTO DEL CIRCULO
QUE LA PRESENTE COPIA ES FIEL Y ORIGINAL DEL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO

1. - **IDENTIFICACIÓN** y si es el caso **NUEVA IDENTIFICACIÓN** al: (en blanco)

DENOMINACIÓN: SANOFI **SIGLA:** (en blanco)

1 bis. - ANTIGUA IDENTIFICACIÓN en caso de modificación:

DENOMINACIÓN: (en blanco) SIGLA: (en blanco)

Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

SEDE: 174, AVENUE DE FRANCE, 75013 PARIS

Nº SIRET: (en blanco)

2. - **FORMA JURÍDICA**: Sociedad Anónima

PRINCIPALES ACTIVIDADES DE LA EMPRESA: TOMA DE PARTICIPACIONES EN CUALQUIER SOCIEDAD O COMPAÑÍA EN LOS CAMPOS DE LA SALUD Y DE LA QUÍMICA ETC...

NUMERO DE ASALARIADOS de la empresa (el día del la diligencia) : 1.244

Fecha de modificación: (en blanco)

3. - NOMBRE COMERCIAL: (en blanco)

CAPITAL: 2.659.121.675 FF. o si es una sociedad con capital variable, monto máximo: (en blanco)

DURACIÓN de la persona jurídica : (en blanco)

En caso de una sociedad sometida a publicidad anual de sus cuentas, FECHA DE CIERRE del ejercicio social: (en blanco)

Fecha de modificación : (en blanco)

COBO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA
02 DIC 2003
JUAN MANUEL SOTO MEDINA
NOTARIO

4. - DIRIGENTES y si es el caso, ADMINISTRADORES, REVISORES FISCALES y SOCIOS comprometidos en forma indefinida y solidaria con las deudas sociales, MIEMBROS del GIE, LIQUIDADORES.

Para el **establecimiento** anteriormente descrito si es necesario, la(s) Persona(s) que tiene(n) el poder de comprometer con su firma la responsabilidad de la empresa (APODERADOS), PROPIETARIOS INDIVISOS DEL FONDO.

244/01

Traducción Oficial No.
JEAN - JACQUES M. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2480/91

Nombre y apellido o denominación : (n blanco)

Domicilio o dirección de la sede : (en blanco)

Antigua calidad : (en blanco)

Nueva o actual calidad : (en blanco)

Fecha de nacimiento : (en blanco)

Lugar de nacimiento : (en blanco)

Nacionalidad : (en blanco)

Nuevo:_____ Saliente: _____ Mantenido pero modificado: ____

Fecha de la modificación : (en blanco)

Lista a continuación sobre anexos: SI _____ O _____

5. - En caso de DISOLUCIÓN: la sociedad continua su explotación para las necesidades de la liquidación: SI_____ NO _____ precisar en el cuadro DIRIGENTES las referencias del (de los) LIQUIDADOR(ES). Indicar el título y la fecha del periódico de avisos legales que publicó el nombramiento del (de los) liquidador(es):

6. - En caso de TRASLADO de la SEDE en la incumbencia de otro Tribunal, indicar los SECRETARIADOS DE TRIBUNALES donde eventualmente se encuentran suscritas las matrículas segundarias: (en blanco)

Lista a continuación sobre páginas adicionales: SI _____ NO

COMO NOTARIO ADJUNTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL
02 DIC 2003
JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

244/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Minjusticia No. 2680/91

7. - En caso de MODIFICACIÓN del CAPITAL luego de una FUSIÓN _____ o ESCISIÓN _____, personas jurídicas que participaron en la operación (denominación, forma jurídica, dirección de la sede, No. R.C.S.) :

Lista a continuación sobre páginas adicionales: SI _____ NO _____

8. - (en blanco)

8. bis – (en blanco)

*SI EL REQUISITO SE REFIERE A UN ESTABLECIMIENTO, OBLIGATORIAMENTE SE DEBE DILIGENCIAR LOS **PUNTOS MARCADOS DE NEGRO***

9. - **ESTABLECIMIENTO INVOLUCRADO, y si es el caso, NUEVA IDENTIFICACIÓN**

al: 01/09/1998

DIRECCIÓN :174, Avenue de France, 75013 Paris

No. SIRET : (en blanco)

COBO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL GUT[illegible]COLDINA
NOTARI[illegible]

9bis. - ANTIGUO ESTABLECIMIENTO en caso de traslado

ANTIGUA DIRECCIÓN en caso de cambio según decisión de la junta municipal

DIRECCIÓN: 32/34 Rue Marbeuf 75008 Paris

En caso de TRASLADO de la SEDE o del ESTABLECIMIENTO, No. SIRET: (en blanco)

En caso de cese de actividad de cualquier asalariado, fecha: (en blanco)

Mantenimiento de una actividad en la antigua sede: SI _____ NO__X___

244/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

10. - Este establecimiento es (para la compañía):

nuevo __X__ modificado _____ suprimido _____

CATEGORÍA(S): sede __X__ establecimiento principal __X__

establecimiento segundario _____

ENSEÑA: (en blanco)

ANÁLISIS DE LA MODIFICACIÓN REALIZADA

11. - En caso de APERTURA del establecimiento, de MODIFICACIÓN DEL MODO DE EXPLOTACIÓN, de ADJUNCIÓN DE ACTIVIDAD, precisar:

Fecha de modificación: 11/09/98

ORIGEN:

Creación __X__ transferencia de actividad _____ compra _____

aporte _____ recuperación después de alquiler en gerencia _____

toma de alquiler en gerencia _____ otros (precisar) _____

Identidad del COMERCIANTE ANTERIOR: (en blanco)

No. R.C.S. o SIREN: (en blanco)

Si hay lugar, fecha de cancelación o modificación en el RCS del comerciante anterior: (en blanco)

CORO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
02 DIC 2003
JUAN MANUEL BOTERO MEDINA
NOTARIO

12. - En caso de CIERRE del establecimiento, de MODIFICACIÓN DEL MODO DE EXPLOTACIÓN, de SUPRESIÓN DE ACTIVIDAD, precisar:

Fecha de la modificación: 01/09/1998

244/01

Traducción Oficial No.
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCÉS - ESPAÑOL
Res. Ministerio No. 2480/91

DESTINO:

desaparición __X__ traslado de actividad _____ venta _____

aporte _____ recuperación por parte del dueño _____

puesta en alquiler gerencia _____ otros (precisar) _____

(primera palabra ilegible) establecimiento segundario

Identidad del BENEFICIARIO: (en blanco)

En caso de ADQUISICIÓN del FONDO (mediante COMPRA o APORTE) señalar el título y la fecha del periódico de avisos legales que publicó la cesión: (en blanco)

En caso de TOMA DE ALQUILER DE GERENCIA, indicar la duración del contrato (en blanco) y si es renovable mediante reconducción tácita: SI _ NO __

Identidad del ALQUILADOR del FONDO: (en blanco)

13. ACTIVIDADES EJERCIDAS en este establecimiento el día de la diligencia:

permanentes _____ temporales _____ ambulantes _____

a consecuencia de: - inicio de explotación _____

- modificación de explotación _____

- fin de explotación _____

14. **ACTIVIDAD PRINCIPAL** : (en blanco)

ACTIVIDADES SEGUNDARIAS : (en blanco)

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

02 DIC 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

15. (en blanco)

Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAROL
Res. Ministerio No. 2680/91

16. (en blanco)

17. Eventuales observaciones del declarante u otra(s) modificación(es): (en blanco)

18. DIRECCIÓN PERMANENTE: (para la correspondencia): 174, Avenue de France, 75013 Paris

LES PETITES AFFICHES (ML) 2, RUE MONTESQUIEU, 75001 PARIS

19. EL SUSCRITO **apoderado** solicita que el presente documento constituya una solicitud de:

- **INSCRIPCIÓN** en el RCS ____X____ , en el RM _____ en el RSAC_____ en el REBA_____ ,

- **CANCELACIÓN** en el RCS_____ en el RM_____ en el RSAC _____ en el REBA_____

y una declaración a los Servicios Fiscales, Organismos del Seguro Social, INSEE y si es o deja de ser EMPLEADOR, en la Inspección del Trabajo y en el ASSEDIC.

Dado en Paris, el 23 de septiembre de 1998. Firma ilegible.

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

02 DIC 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

Sello: Copia certificada con fecha del 09/10/01. Por el Director General del INPI, firma ilegible del Jefe de Departamento.

Sello: Instituto Nacional de la Propiedad Industrial - República Francesa.

Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAROL
Res. Ministerio No. 2680/91

Sello: Ministerio de Economía, Hacienda e Industria - Instituto Nacional de la Propiedad Industrial – República Francesa.

Sello: Tribunal de Comercio de Paris con fecha del 24 de septiembre de 1998. Nº. de radicación: 51141

APOSTILLA
(Convención de La Haya del 5 de octubre de 1961)

1. República Francesa

   El presente acta público

2. Ha sido firmado por (ilegible)
3. Actuando en calidad de (ilegible)
4. Con sello de (ilegible)

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS
18 OCT 2001

Certificado

5. En Paris 6. El 15 de octubre del 2001
7. Por el Fiscal General ante el Tribunal Superior
8. Bajo el número 70583
9. Sello / estampilla: Tribunal Superior de Paris – Fiscalia – Republica Francesa.
10. Firma ilegible.

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA
2001 NOV 13 P 12:23
NO SE ASUME RESPONSABILIDAD DEL TEXTO

COMO NOTARIO TERCERO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE DADO A LA VISTA
02 DIC 2001
JUAN MANUEL BOTERO MEDINA
NOTARIO

Es traducción fiel y completa de la cual se deja copia en los archivos de esta oficina para confrontación y a la cual me remito.
Traducción oficial No. 244/01
COLO: 00751-805-001-3
Traductor: Jean-Jacques Turpin.
Bogotá, D.C., 06 de noviembre del 2001.

Traducción Oficial No. 244/01
JEAN - JACQUES H. TURPIN
Traductor e Intérprete Oficial
FRANCES - ESPAÑOL
Res. Ministerio No. 2680/91

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADOS CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 13 NOV. 2001

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

02 DIC 2003

JUAN MANUE... NU...

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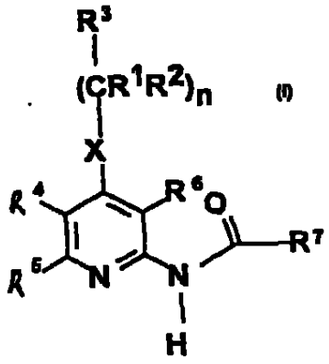


(I)

(57) Abstract: Compounds of general formula (I), wherein R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; are strong adenosine A_3 receptor ligands preferably antagonists.

WO 02/096879 A1

AMINOQUINOLINE AND AMINOPYRIDINE DERIVATIVES AND THEIR USE AS ADENOSINE A3 LIGANDS

The present invention relates to adenosine A_3 receptor ligands of the general formula (I), within those preferably antagonists, as well as their salts, solvates and isomers, and the pharmaceutical compositions containing them, to the use of the compounds of the general formula (I), as well as their salts, solvates and isomers, to the preparation of the compounds of the general formula (I) and their salts, solvates and isomers, furthermore to the new intermediates of the general formulae (II) (III) and (IV) and to the preparation thereof.

Adenosine is a well-known component of several endogenous molecules (ATP, NAD^+, nucleic acids). Besides, it plays an important regulatory role in many physiological processes. The effect of adenosine on heart function was discovered already in 1929. (Drury and Szentgyörgyi, J Physiol 68:213, 1929). The identification of an increasing number of physiological functions mediated by adenosine and the discovery of new adenosine receptor subtypes give possibilities for therapeutic application of specific ligands (Poulse, S. A. and Quinn, R. J. Bioorganic and Medicinal Chemistry 6:619, 1998).

To date, the receptors for adenosine have been classified into three main classes: A_1, A_2 and A_3. The A_1 subtype is partly responsible for inhibiting the adenylate cyclase by coupling to G_i membrane protein, partly influences other second messenger systems. The A_2 receptor subtype can be subdivided into two further subtypes – A_{2a} and A_{2b} -, which receptors stimulate the adenylate cyclase activity. The sequence of adenosine A_3 receptors have been recently identified from rat testis cDNA library. Later it was proved that it corresponds to a novel, functional adenosine receptor. The activation of the A_3 receptors is connected also with several second-messenger systems: inhibiting of adenylate cyclase, stimulating of phospholipase C and D.

The adenosine receptors are found in several organs and regulate their functions. Both A_1 and A_{2a} receptors play important roles in the central nervous system and cardiovascular system. In the CNS, the adenosine inhibits the release of synaptic transmitters which effect is mediated by A_1 receptors. In the heart, also the A_1 receptors mediate the negative inotropic, chronotropic and dromotropic effects of adenosine. The adenosine A_{2a} receptors located relatively in a higher amount in the striatum, display a

functional interaction with dopamine receptors in regulating the synaptic transmission. The A_{2a} adenosine receptors on endothelial and smooth muscle cells are responsible for adenosine-induced vasodilation.

On the basis of mRNA identification, the A_{2b} adenosine receptors are widely distributed in different tissues. They have been identified almost in every cell type, but its expression is the highest in the intestine and the bladder. This subtype probably also has important regulatory function in the regulation of the vascular tone and plays a role in the function of mast cells.

Contrary to A_1 and A_{2a} receptors, where the tissue distribution was detected on the protein level, the presence of A_{2b} and A_3 receptors was detected on the basis of their mRNA level. Expression levels for A_3 adenosine receptors are rather low comparing to other subtypes and highly species dependent. A_3 adenosine receptors are expressed primarily in the central nervous system, testis, immune system and appear to be involved in the modulation of mediator release from mast cells in immediate hypersensitivity reaction.

The A_3 antagonists published so far in the literature belong to the groups of flavonoides, 1,4-dihydropyridine derivatives, triazoloquinazolines, thiazolonaphthyridines and thiazolopyrimidines. The present invention relates to a novel type of effective A_3 antagonists, which have the aminoquinoline structure.

For therapeutic use it is essential to ensure that the molecule does not bind, or bind only in the case of very high concentration to the A_1, A_{2a} and A_{2b} sub-types of the adenosine receptor. Our present invention relates to the compounds of the general formula (I) as well as their salts, solvates and isomers which have great selectivity for the A_3 sub-type of the adenosine receptor.

Our aim was to prepare A_3 ligands first of all with quinoline structure, and within those preferably antagonists, which have strong antagonistic effect and show high selectivity for the A_3 receptor, ie. they inhibit the A_3 receptor in much lower concentration than they inhibit the A_1, A_{2a} and A_{2b} receptors. Further aims were to have stability, bioavailability, therapeutic index and toxicity data which make possible to develope the new compounds into drug substances and that due to their favourable enteral absorbtion the compounds can be applied orally.

We have found that the compounds of the general formula (I) - wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for a 5- or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom-

optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group. straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom, or for a 5 or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom,

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 – and their salts, solvates, and isomers and the salts, solvates of the latter, fulfill the above criteria.

Detailed meanings of the above listed substituents are as follows:

By a straight or branched C_{1-4} alkyl group we mean methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, secondary-butyl-, terciary-butyl-, preferably ethyl- or methyl group.

By a straight or branched C_{1-4} alkoxy group we mean methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, secondary-butoxy-, terciary-butoxy-, preferably ethoxy- or methoxy group.

By a C_{3-6} cycloalkyl group we mean cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexyl group.

By 1,3-butadienyl-group we mean (-CH=CH-CH=CH-)-group, ie. the pyridine ring substituted by R^4 and R^5 substituents means a benzopyridine ring or by its trivial name a quinoline ring.

The heteroaromatic ring containing one or two or three nitrogen atoms means pyrrol, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyrimidine, pyridazine, pyrazine and 1,3,4-triazine ring. The ring is optionally substituted by a C_{1-4} alkyl, or alkoxy group or by a halogen atom.

The heteroaromatic ring containing one nitrogen atom and one oxygen or sulphur atom means oxazole, isoxazole, thiazole, isothiazole ring. The ring is optionally substituted by a C_{1-4} alkyl, or alkoxy group or by a halogen atom.

Salts of the compounds of the general formula (I) mean salts given with inorganic and organic acids and bases. Preferred salts are those given with pharmaceutically accepted acids as for instance hydrochloric acid, sulphuric acid, ethanesulphonic acid, tartaric acid, succinic acid, fumaric acid, malic acid, citric acid, and bases, as for instance sodium hydroxide, potassium hydroxide, ethanolamine.

Solvates mean solvates given with various solvents, as for instance with water or ethanol.

The compounds of the general formula (I) show geometric and optical isomerism, therefore the invention also relates to mixtures of the geometric isomers, to racemic or optically active geometric isomers, as well as to their salts and solvates.

A favourable group of the compounds of the general formula (I) is formed by the compounds of the general formula (IA), wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for a 5- or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^9, R^{10}, R^{11}, and R^{12} independently mean hydrogen atom or straight or branched C_{1-4} alkyl group, or straight or branched C_{1-4} alkoxy group, or hydroxy group or halogen atom, or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylenedioxy group;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom, or for a 5 or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom,

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts, solvates, optically active isomers and the salts, solvates thereof.

A favourable group of the compounds of the general formula (IA) is formed by the compounds wherein

R^1 stands for hydrogen atom, or methyl group;

R^2 stands for hydrogen atom, or methyl group;

R^3 stands for phenyl- or thienyl- or furyl group;

R^9, R^{10}, R^{11}, and R^{12} mean independently hydrogen atom or straight or branched C_{1-4} alkyl group, or straight or branched C_{1-4} alkoxy group, or hydroxy group or halogen atom, or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylenedioxy group;

R^6 stands for hydrogen atom, or cyano group;

R^7 stands for 4-methoxyphenyl-, 3-methylphenyl-, 3-methoxyphenyl-, 3-thienyl-, or 3-furyl-group,

X stands for -NH-group or for oxygen atom and

n stands for 1 –

and their salts, solvates, optically active isomers and the salts, solvates thereof.

Especially favourable are the following compounds complying with the above criteria:

3-methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

3-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

3,4-methylenedioxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide;

N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide;

4-methoxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide;

3,4-methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-benzamide;

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide;

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide,

and their salts, solvates, optically active isomers and the salts, solvates thereof.

According to another of its aspects, the present invention also relates to pharmaceutical compositions containing as active principles the compounds of the general formula (I) or their isomers, salts and solvates, which are preferably oral compositions, but

inhalable, parenteral and transdermal formulations are also subjects of the invention. The above pharmaceutical compositions may be solids or liquides, such as tablets, pellets, capsules, patches, solutions, suspensions or emulsions. The solid compositions, first of all tablets and capsules are the preferred pharmaceutical forms.

The above pharmaceutical compositions are prepared by applying usual pharmaceutical excipients and by using standard methods.

The compounds of the general formula (I) can be used in treating pathologies, in the development of which A_3 receptor plays a role.

The compounds of the present invention having selective activity on the A_3 receptor can be used in the therapeutic and/or preventive treatment of disfunctions of the heart, kidney, respiratory system, central nervous system. They inhibit the protective effect of adenosine in growing tumor cells, prevent mast cell degranulation, inhibit the cytokine production, reduce the inraocular pressure, inhibit the TNFα release, inhibit the migration of eosinophils, neutrophils and other immune cells, inhibit the bronchoconstriction and plasma extravasation.

Based on these effects, adenosine A_3 receptor antagonists of the present invention may be therapeutically useful as antiinflammatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing drugs. They also may be useful in the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison's disease, Crohn's disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes (K. N. Klotz, Naunyn-Schmiedberg's Arch. Pharmacol. 362:382, 2000; P. G. Baraldi és P. A. Borea, TiPS 21:456, 2000).

The compounds of the present invention may be preferable used for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrythmia and renal diseases.

According to another of its aspects, the present invention relates to the use of the compounds of the general formula (I) in the treatment of the above pathologies. Suggested

daily dose is 1-100 mg active ingredient depending on the nature and severeness of the disease and on sex, weight etc. of the patient.

Further subject of the invention is the preparation of the compounds of the general formula (I) and of the intermediates of the general formulae (II) (III) and (IV).

The intermediates of the general formulae (II) (III) and (IV) which are used in the preparation process according to the invention, are novel. Substituents of the general formulae (II), (III) and (IV) have the meanings as defined above.

In the process according to our invention the bis-carboxamide of the general formula (II) is selectively hydrolysed and the resulting compound of the general formula (I) is, if desired, transformed into its salts, solvates or, liberated from its salt, solvate and separated into its geometric or optical isomers.

Substituents of the compounds of the general formula (I) may be transformed into each other by known methods.

Selective hydrolysis is performed by using alcoholic, preferably methanolic alkali hydroxide solution, preferably potassium and/or sodium hydroxide solutions, but other agents helping the hydrolysis of amides can also be used.

The selective hydrolysis can be carried out in a wide temperature range, favourably between 20 °C- 100 °C.

The compounds of the general formula (II) –wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are as defined above – can be obtained by several known methods, among them the one demonstrated in Scheme 1 (Figure 6), by acylation of the compounds of the formula (III), by using an acylation method known in the organic chemistry. For acylating agent preferably acyl chloride, for acid binding agent triethylamine and/or pyiridine can be applied, but other acid binding agents can also be used.

The compounds of the general formula (III) – wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n are as defined above – can be prepared from the compounds of the formula (IV) - by using methods known per se (Nan Zhang, Bioorg. and Med. Chem. Lett., 10, 2825, 2000).

The compounds of the general formula (IV) – wherein the meanings of R^4, R^5 and R^6 are as defined above – can be prepared from the compounds of the formula (V), by using methods known per se (D.L. Leysen, J. Heterocyclic Chem., 24, 1611, 1987).

The compounds of the general formula (V) – wherein the meanings of R^4, R^5 and R^6 are as defined above – can be prepared from the compounds of the formula (VI), by using methods known per se (Pfizer (Inc) USP 4,175,193) .

The compounds of the invention, of the general formulae (I), (II), (III) and (IV), their preparation and biological activity are demonstrated in the following Examples, without limiting the scope of claims to the Examples.

Figure 1 shows general formula (I), Figure 2 shows general formula (IA), Figure 3 shows general formula (II), Figure 4 shows general formula (III) and Figure 5 shows general formula (IV). Figure 6 shows Scheme 1 the reaction route for the preparation of compounds of the general formula (I).

Examples

Example 1

3-Methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide:

In general formula (I) R^1 and R^2 stand for hydrogen atoms, R^3 for phenyl group, R^4 and R^5 form together a 1,3-butadienyl group, R^6 stands for cyano group, R^7 for 3-methylphenyl group, the meaning of X is –NH group, n is 1.

a.) 2-Amino-3-cyano-4-chloroquinoline:

The mixture of 10 g of 2-amino-3-cyano-4-hydroxyquinoline and 15 ml of phosphoryl chloride is heated under stirring at 110 °C. The reaction mixture is cooled down, poured onto 100 ml of ice-water and neutralized with 60 ml of 10 % sodium hydroxide solution. The resulting yellow precipitate is filtered off, washed with 50 ml of water. After drying 7.5 g of the title compound is obtained, mp.: 210 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 7.21 ppm, (s, 2H, NH_2), 7.35-7.40 ppm, (dd, 1H, 6-H), 7.53-7.57 ppm, (d, 1H, 5-H), 7.70-7.75 ppm, (dd, 1H, 7-H), 7.93-7.98 ppm, (d, 1H, 8-H)

b.) 2-Amino-3-cyano-4-benzylaminoquinoline

5 g of 2-amino-3-cyano-4-chloroquinoline and 11 ml of benzylamine are heated under stirring at 130 °C. The reaction mixture is poured onto 50 ml of water, the resulting precipitate is filtered off, washed with 50 ml of water. The pale-yellow precipitate is recrystallized from dimethylformamide to obtain 5.2 g of the title compound.
Mp.: 206 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 5.02-5.03 ppm, (d, 2H, N-CH_2), 6.22 ppm, (s, 2H, NH_2), 7.14-7.16 ppm, (dd, 1H, 6-H), 7.24-7.26 ppm,(dd,1H, 5-H), 7.30 ppm, (s, 5H, Ph), 7.50-7.52 ppm, (dd, 1H, 7-H), 8.16-8.19 ppm, (d, 1H, 8-H), 8.30-8.33 ppm, (t, 1H, NH)

Using 2-aminomethylpyridine or 3-aminomethylpyridine or 4-aminomethylpyridine instead of benzylamine, the appropriate compounds of general formula III can be obtained.

c.) 3-Methyl-N-(3-methylbenzoyl)-N-(4-benzylamino-3-cyanoquinoline-2-yl)benzamide:
To the solution of 5 g of 2-amino-3-cyano-4-benzylaminoquinoline in 30 ml of pyridine 6 ml of 3-methylbenzoyl chloride are dropped, under stirring at 0°C. The reaction mixture is stirred at 80 °C for 8 hour, then it is poured onto 150 ml of ice-water. The precipitate is filtered off, washed twice with 40 ml of water. The resulting white crystalline material is recrystallized from 200 ml of ethanol to give 9.2 g of the title compound, mp.: 234 °C

By using pyridine-3-carbonyl chloride as acylating agent, the appropriate compound of general formula II can be obtained.

d.) 3-Methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide
To the solution of 5 g of 3-methyl-N-(3-methylbenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide in 80 ml of acetonitrile 20 ml of 1N methanolic potassium hydroxide solution are added. The reaction mixture is refluxed for 3 minutes, then 3 ml of glacial acetic acid is added to it, then it is neutralized with 50 ml of 1M sodium hydrogen carbonate solution and the resulting crystals are filtered off. The white crystalline material is recrystallized from 130 ml of acetonitrile to give 3.1 g of the title compound of general formula (I). Mp.: 230 °C.

Example 2
4-Methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide
In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 4-methoxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline, prepared as described in Example 1., is transformed with 4-methoxybenzoyl chloride, analogously as described in Example 1., into 4-methoxy-N-(4-methoxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide, which after selective hydrolysis, by the method described in Example 1., results the title compound of general formula (I). Melting point of the title compound: 188 °C.

Sodium salt of the title compound is prepared by the following method:

4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide is dissolved in methanol and equivalent amount of sodium hydroxide in methanol is added to it. The precipitated white crystalline material is filtered off. Mp.: 255 °C.

Ethanesulfonate salt of the title compound is prepared by the following method:
4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide is dissolved in methanol and equivalent amount of ethanesulfonic acid is added to it. The precipitated white crystalline material is filtered off. Mp.: 223 °C.

Example 3

3-Methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-methoxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline, prepared as described in Example 1., is transformed with 3-methoxybenzoyl chloride, analogously as described in Example 1., into 3-methoxy-N-(3-methoxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide, which after selective hydrolysis by the method described in Example 1., results the title compound of general formula (I). Melting point of the title compound: 186 °C.

Example 4

3,4-Methylenedioxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3,4-methylenedioxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline prepared as described in Example 1., is transformed with 4-methoxybenzoyl chloride analogously as described in Example 1., into 3,4-methylenedioxy-N-(3,4-methylenedioxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide which after selective hydrolysis by the method described in Example 1.,

results the title compound of general formula (I).

Melting point of the title compound: 231 °C.

Example 5

N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 2-thienyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline prepared as described in Example 1. is transfomed with thiophene-2-carbonyl chloride, analogously as described in Example 1., into N-(2-thiophenecarbonyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide, which after selective hydrolysis, by the method described in Example 1., results the title compound of general formula (I).

Melting point of the title compound: 197°C.

Example 6

N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-thienyl group, X means -NH-group, n is 1.

a.) 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline

5 g of 2-amino-3-cyano-4-chloroquinoline, prepared as described in Example 1, is stirred with 11 ml of 2-thienylmethylamine at 130 °C for 3 hours. The reaction mixture is poured onto 50 ml of water, the resulting precipitate is filtered off, washed with 50 ml of water. The pale yellow material is recrystallized from 25 ml of ethanol to obtain 5.2 g of title compound, mp.: 208 °C.

The 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described above is transformed with thiophene-3-carbonyl chloride, analogously as described in Example 1, into N-(3-thiophenecarbonyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-

thiophene-3-carboxamide which after selective hydrolysis, by the method described in Example 1, gives the title compound of general formula (I). Melting point of the title compound: 223 °C.

Example 7

4-methoxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 4-methoxyphenyl group, X means -NH-group, n is 1.

The 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described in Example 6. is transformed with 4-methoxybenzoyl chloride into 4-methoxy-N-(4-methoxybenzoyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide by the method described in Example 1, which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 173 °C.

Example 8

3,4-methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3,4-methylenedioxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described in Example 6. is transformed with 3,4-methylenedioxybenzoyl chloride into 3,4-methylenedioxy-N-(3,4-methylenedioxybenzoyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide by the method described in Example 1, which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 241°C.

Example 9

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-furyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 2-furyl group, X means -NH-group, n is 1.

a.) 2-Amino-3-cyano-4-(2-furylmethylamino)quinoline

5 g of 2-amino-3-cyano-4-chloroquinoline, prepared as described in Example 1 are stirred with 1 ml of 2-furylmethylamine (furfurylamine) at 130 °C for 3 hours. The reaction mixture is poured onto 50 ml of water, the resulting precipitate is filtered off, washed with 50 ml of water. The pale yellow material is recrystallized from 20 ml of ethanol to obtain 4.8 g of the title compound, mp.: 208 °C.

The 2-amino-3-cyano-4-(2-furylmethylamino)quinoline prepared as described above is transformed with furan-2-carbonyl chloride by the method described in Example 1. into N-(2-furancarbonyl)-N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 196 °C.

Example 10

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2yl)thiophene-3-carboxamide

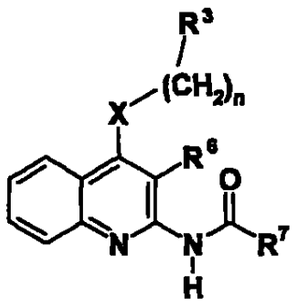
In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-furyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-thienyl group, X means -NH-group, n is 1.

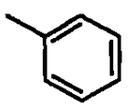
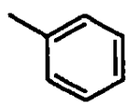
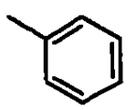
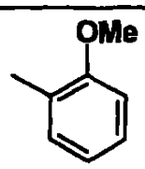
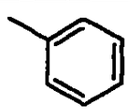
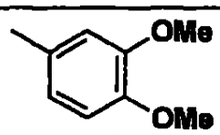
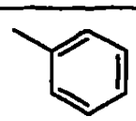
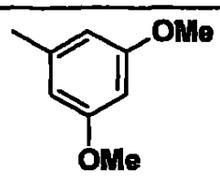
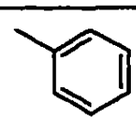
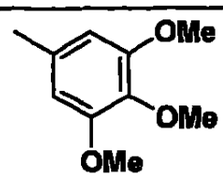
1.

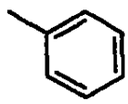
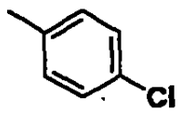
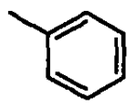
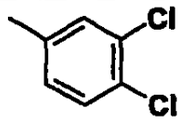
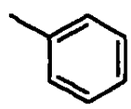
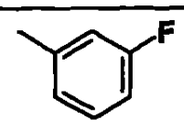
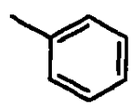
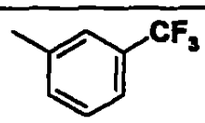
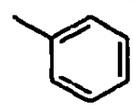
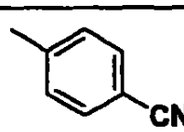
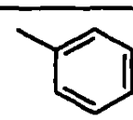
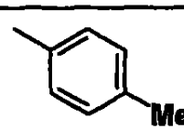
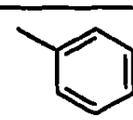
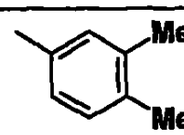
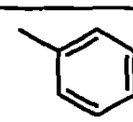
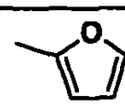
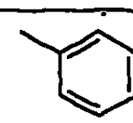
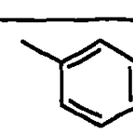
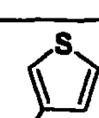
The 2-amino-3-cyano-4-(2-furylmethylamino)quinoline prepared analogously as described in Example 6. is transformed with thiophene-3-carbonyl chloride by the method described in Example 1. into N-(3-thiophene carbonyl)-N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide which after selective hydrolysis, performed analogously as described in Example 1. gives the title compound of general formula (I). Melting point of the title compound: 118 °C.

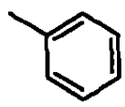
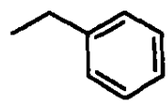
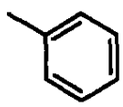
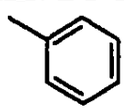
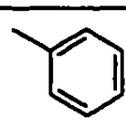
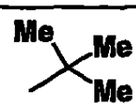
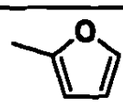
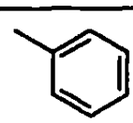
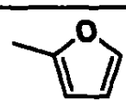
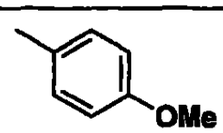
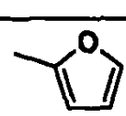
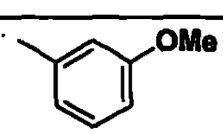
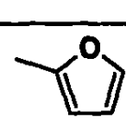
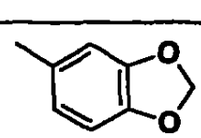
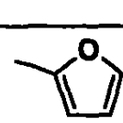
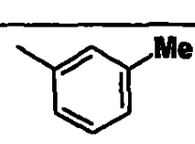
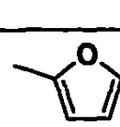
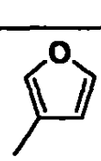
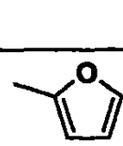
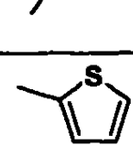
Structure and physical characteristics of further compounds of general formula (I) prepared by the method described in Example 1. are shown in Tables I. and II.

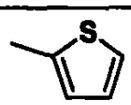
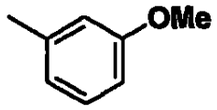
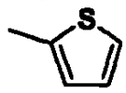
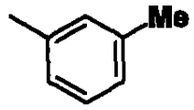
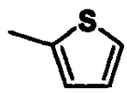
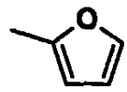
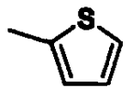
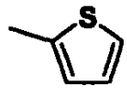
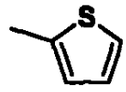
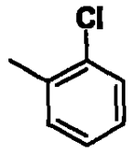
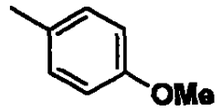
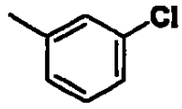
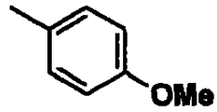
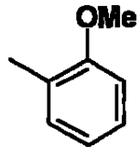
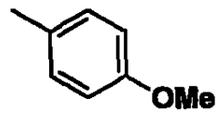
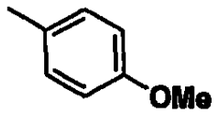
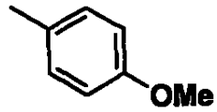
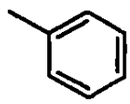
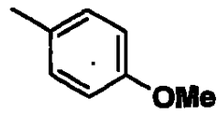
TABLE I.

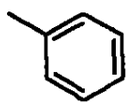
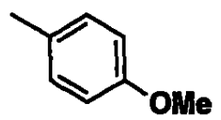
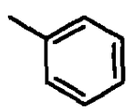
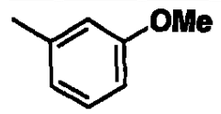
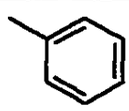
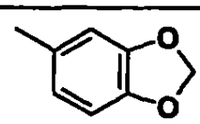
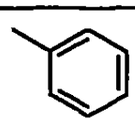
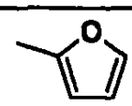
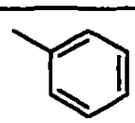
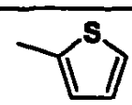
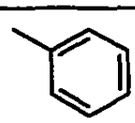
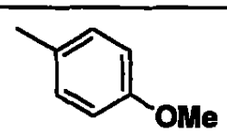
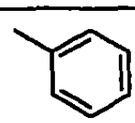
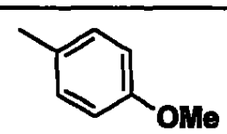
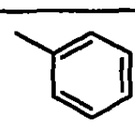
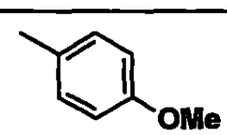
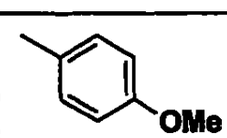
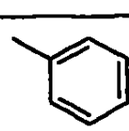
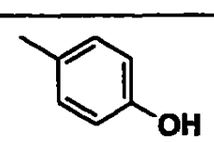


No.:	X	R^3	R^6	R^7	n	Mp [°C]
11.	NH		CN		1	237
12.	NH		CN		1	128
13.	NH		CN		1	116
14.	NH		CN		1	100,5
15.	NH		CN		1	223

16.	NH		CN		1	193,5
17.	NH		CN		1	193
18.	NH		CN		1	208
19.	NH		CN		1	215
20.	NH		CN		1	250
21.	NH		CN		1	205
22.	NH		CN		1	238
23.	NH		CN		1	212
24.	NH		CN		1	215
25.	NH		CN		1	234

26.	NH		CN		1	160,5
27.	NH		CN	—Me	1	184
28.	NH		CN		1	141,5
29.	NH		CN		1	194
30.	NH		CN		1	203
31.	NH		CN		1	152
32.	NH		CN		1	190
33.	NH		CN		1	202
34.	NH		CN		1	207
35.	NH		CN		1	159
36.	NH		CN		1	200

37.	NH		CN		1	206
38.	NH		CN		1	221
39.	NH		CN		1	198
40	NH		CN		1	158
41.	NH		CN		1	178
42.	NH		CN		1	198,5
43.	NH		CN		1	197,5
44.	NH		CN		1	191
45.	NH		CN		1	168,5
46.	N-Me		CN		1	155

47.	NH		H		1	172
48.	NH		H		1	250
49.	NH		H		1	264
50.	NH		H		1	265
51.	NH		H		1	163
52.	O		CN		1	157
53.	S		CN		1	196
54.	S=O		CN		1	205
55.	NH	H	CN		0	266
56.	NH		CN		1	154

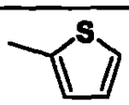
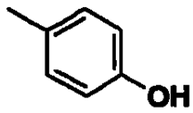
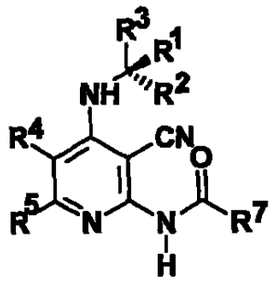
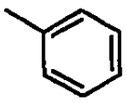
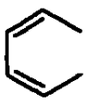
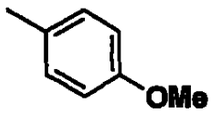
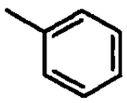
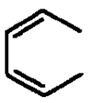
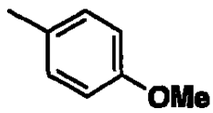
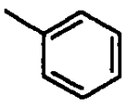
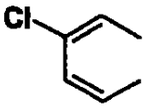
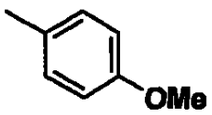
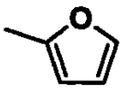
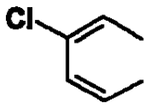
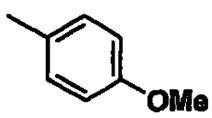
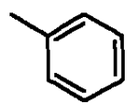
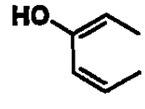
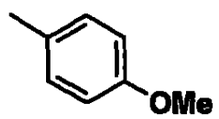
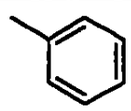
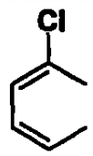
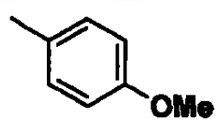
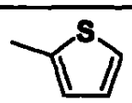
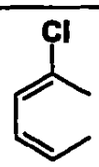
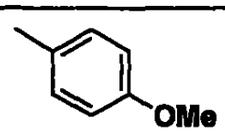
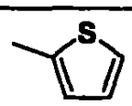
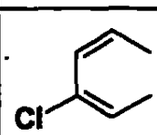
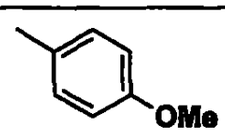
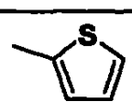
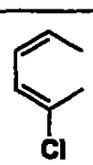
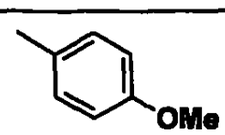
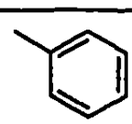
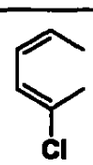
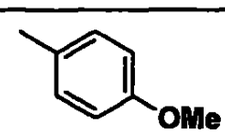
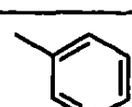
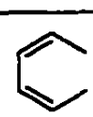
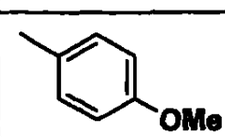
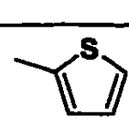
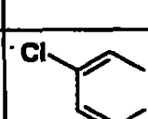
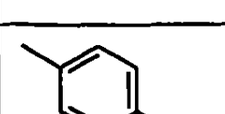
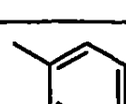
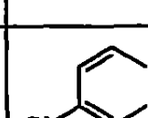
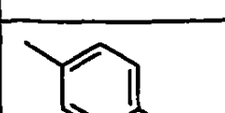
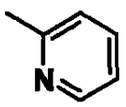
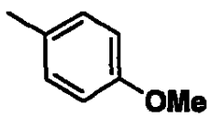
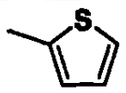
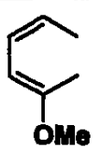
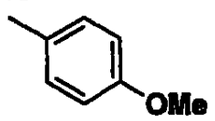
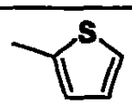
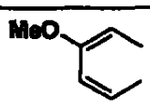
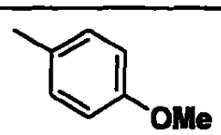
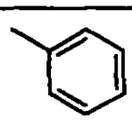
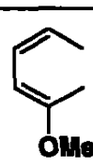
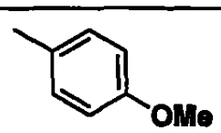
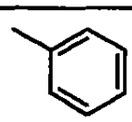
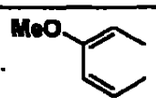
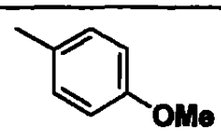
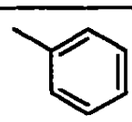
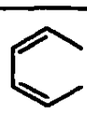
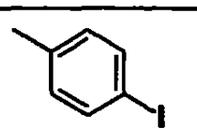
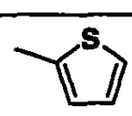
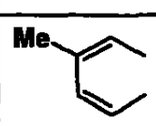
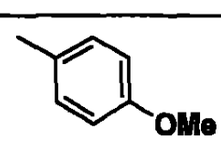
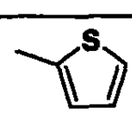
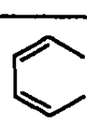
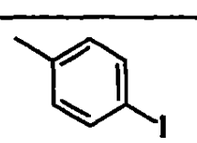
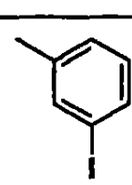
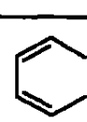
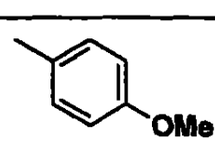
57	NH		CN		1	145

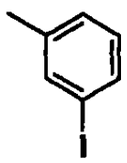
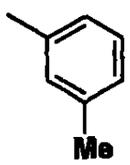
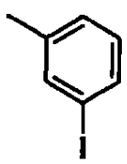
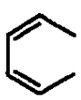
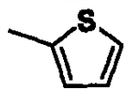
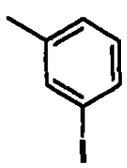
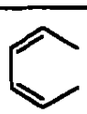
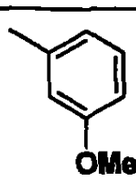
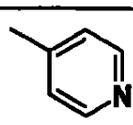
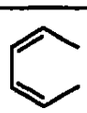
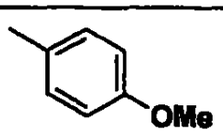
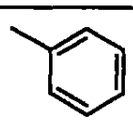
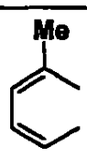
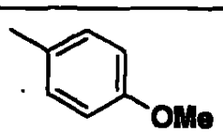
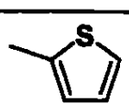
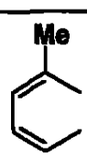
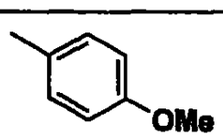
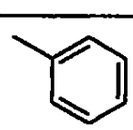
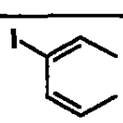
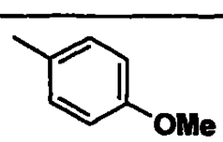
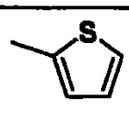
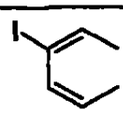
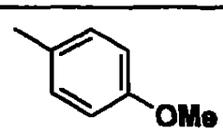
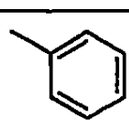
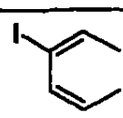
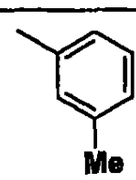
TABLE II.

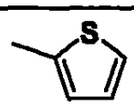
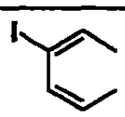
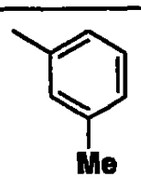
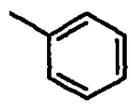
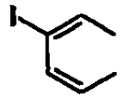
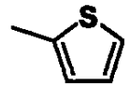
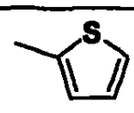
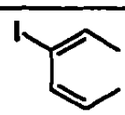
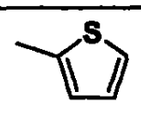
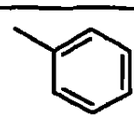
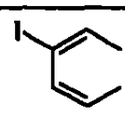
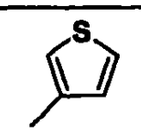
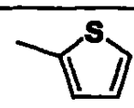
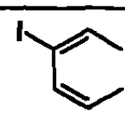
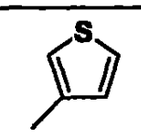
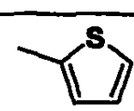
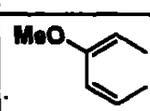
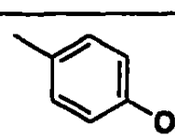
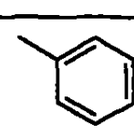
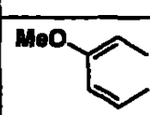
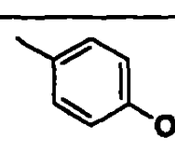
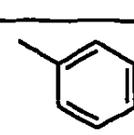
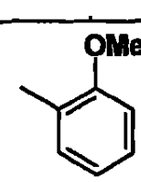
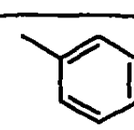
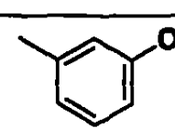
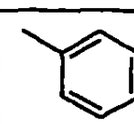
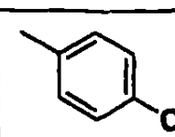


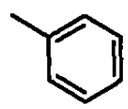
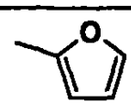
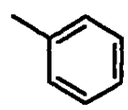
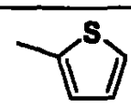
	R^1	R^2	R^3	R^4	R^5	R^7	Mp [°C]
58.	Me	H					165
59.	H	Me					145
60.	H	H					119
61.	H	H					119

62.	H	H				243
63.	H	H				176
64.	H	H				171
65.	H	H				199
66.	H	H				203
67.	H	H				180
68.	H	H				117
70.	H	H				153
71.	H	H				215

72.	H	H				237
73.	H	H				275
74.	H	H				245
75.	H	H				247
76.	H	H				222
77.	H	H				218
78.	H	H				214
79.	H	H				252
80.	H	H				178

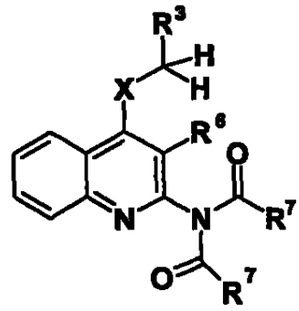
81.	H	H				173
82.	H	H				212
83.	H	H				184
84.	H	H				150
85.	H	H				195.
86.	H	H				171
87.	H	H				217
88.	H	H				149
89.	H	H				135

90.	H	H				127
91.	H	H				257
92.	H	H				260
93.	H	H				153
94.	H	H				145
95.	H	H				214
96.	H	H				183
97.	H	H		H	H		167
98.	H	H		H	H		162
99.	H	H		H	H		183

100	H	H		H	H		216
101	H	H		H	H		206

Structure and physical characteristics of intermediates of general formula (II) prepared by the method described in Example 1. are shown in Table III.

TABLE III.



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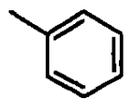
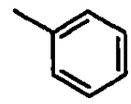
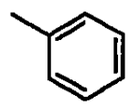
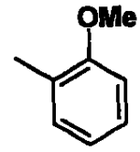
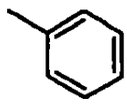
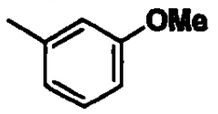
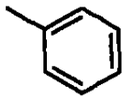
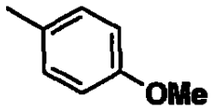
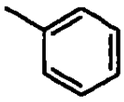
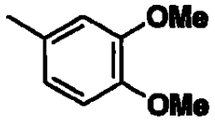
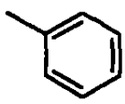
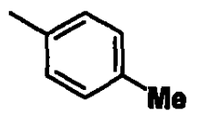
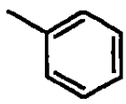
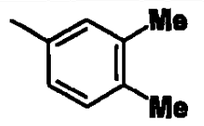
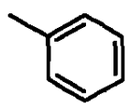
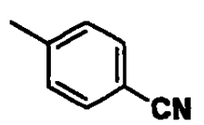
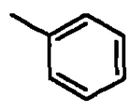
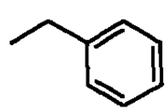
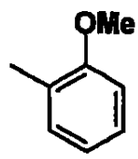
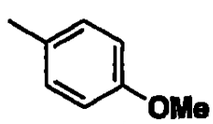
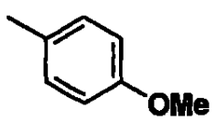
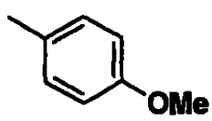
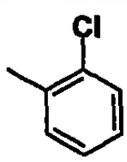
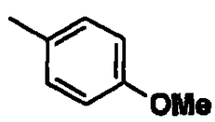
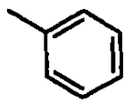
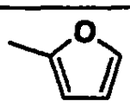
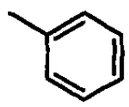
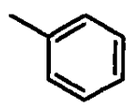
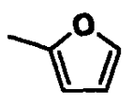
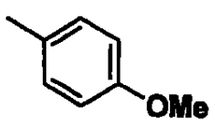
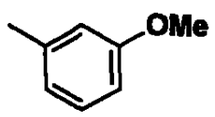
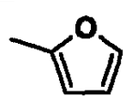
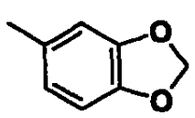
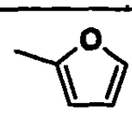
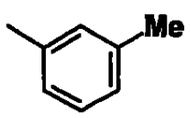
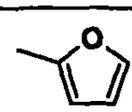
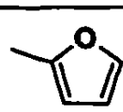
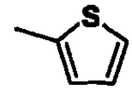
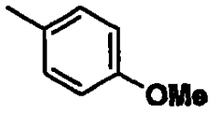
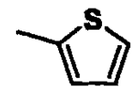
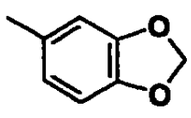
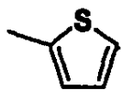
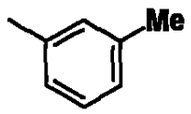
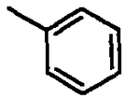
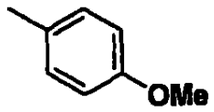
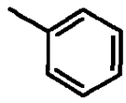
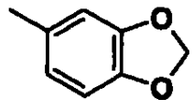
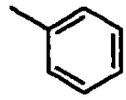
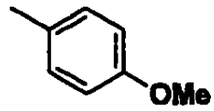
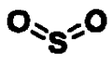
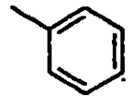
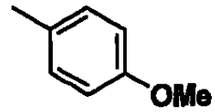
102	NH		CN		213
103.	NH		CN		208

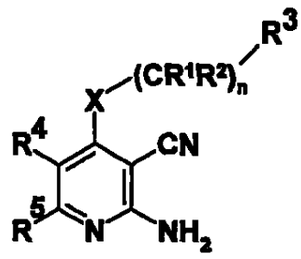
104	NH		CN		178s
105	NH		CN		158
106	NH		CN		210
107	NH		CN		223
108	NH		CN		224
109	NH		CN		212
110	NH		CN		198
111	NH		CN		208
112	NH		CN		168
113	NH		CN		168

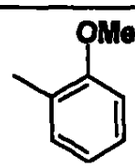
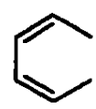
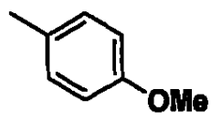
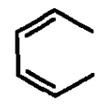
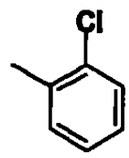
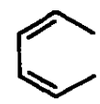
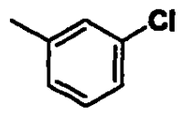
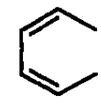
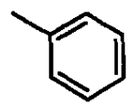
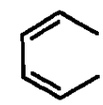
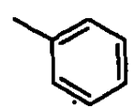
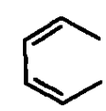
114	NH		CN		225
115	NH		CN	Me	152
116	NH		CN	Et	192
117	NH		CN		177
118	NH		CN		169
119	NH		CN		151
120	NH		CN		218
121	NH		CN		194
122	NH		CN		188
123	NH		CN		179

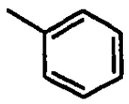
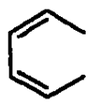
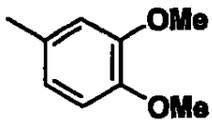
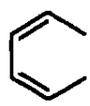
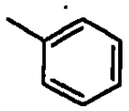
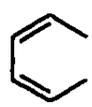
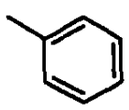
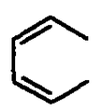
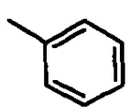
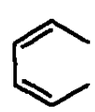
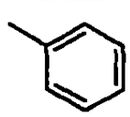
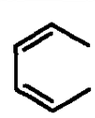
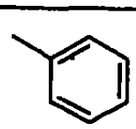
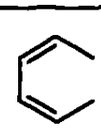
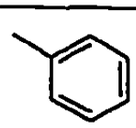
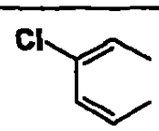
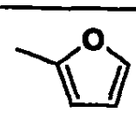
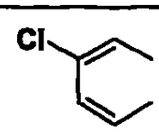
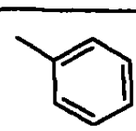
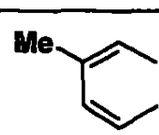
124	NH		CN		239
125	NH		H		162
126	NH		H		262
127	S		CN		170
128			CN		228

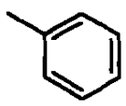
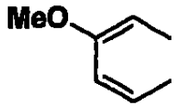
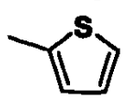
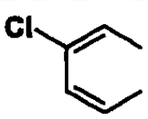
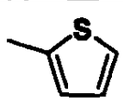
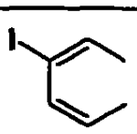
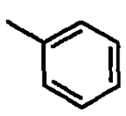
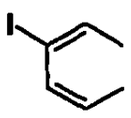
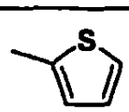
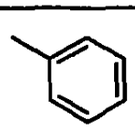
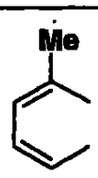
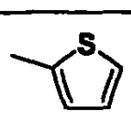
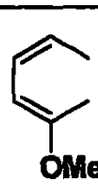
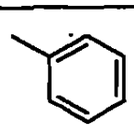
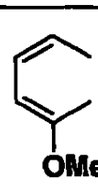
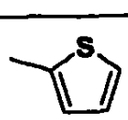
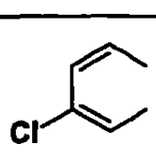
Structure and physical characteristics of intermediates of general formula (III) and (IIIa) prepared by the method described in Example 1. are shown in Table IV.

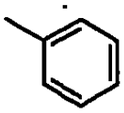
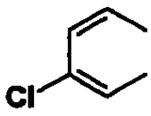
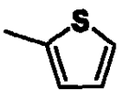
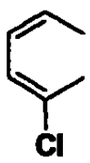
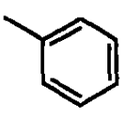
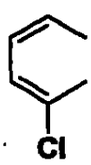
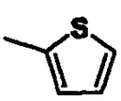
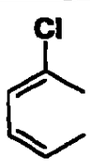
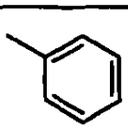
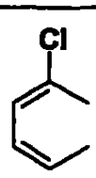
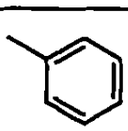
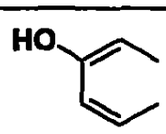
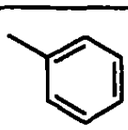
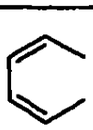
TABLE IV.



No.:	R^1	R^2	R^3	R^4	R^5	X	n	Mp [°C]
129	H	H				NH	1	192
130	H	H				NH	1	202
131	H	H				NH	1	250
132	H	H				NH	1	167
133	H					NH	1	183
134	H					NH	1	182

135	H	H			NH	2	172
136	H	H			NH	2	143
137	H				NH	2	129
138	H				NH	2	136
139	H	H			N-Me	1	212
140	H	H			S	1	168
141	H	H			O	1	213
142	H	H			NH	1	234
143	H	H			NH	1	221
144	H	H			NH	1	198

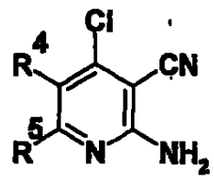
145	H	H			NH	1	201
146	H	H			NH	1	213
147	H	H			NH	1	198
147	H	H			NH	1	201
148	H	H			NH	1	167
149	H	H			NH	1	156
150	H	H			NH	1	187
151	H	H			NH	1	178
152	H	H			NH	1	207

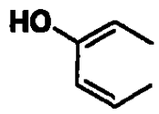
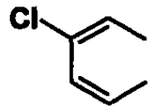
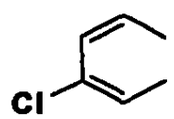
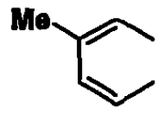
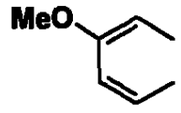
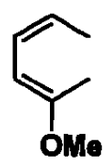
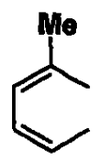
153	H	H			NH	1	217
154	H	H			NH	1	204
155	H	H			NH	1	216
156	H	H			NH	1	205
158	H	H			NH	1	213
159	H	H			NH	1	200
160					NH	0	214

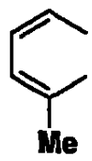
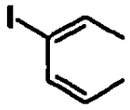
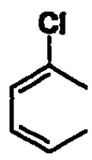
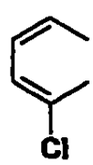
Structure and physical characteristics of intermediates of general formula (V) prepared by the method described in Example 1. are shown in Table V.

5

TABLE V.



No:	R^4 R^5	Mp [°C]
161.		360
162.		250
163.		278
164		283
165.		360
166.		234
167		246

168		267
169		293
170		289
171		307

Example 172.

Tablets of the following composition are made by known methods used in the pharmaceutical industry

Active ingredient	25 mg
Lactose	50 mg
Avicel	21 mg
Crospovidone	3 mg
Magnesium stearate	1 mg

Biology

Methods

Human adenosine A_3 receptor binding

Preparing membrane suspension: collect CHO cells expressing hA3 receptors by washing three times with ice cold PBS, centrifugate at 1000 x g 10 min, homogenize for 15 sec in buffer (50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, pH 8.0), centrifugate at 43.000 x g for 10 min (Sigma 3K30), suspense the membrane preparation in the buffer mentioned above, store the aliquots at -80 C.

Binding protocol: incubate CHO-hA_3 membrane preparation (2 µg protein content) in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, 3 U/mL adenosine deaminase, pH 8.0), in the presence of 0.5 nM [^{125}I]AB-MECA (p-amino-benzyl-methylcarboxamido-adenosine) (100.000 cpm) and 100 µM R-PIA (N^6-[L-2-phenylisopropyl]adenosine) to define non-specific binding or test compound in a total volume of 50 µL for 1 hr at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked in 0.5% polyethylenimine for 3 hours), wash 4x with 1 mL ice-cold 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA (pH 8.0) on 96-well Brandel Cell Harvester. Detection of activity: in gamma-counter (1470 Wizard, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Human adenosine A_1 receptor binding

Preparing membrane suspension: collect CHO cells expressing hA_1 receptors by washing three times with ice cold PBS, centrifugate at 1000 x g 10 min, homogenize for 15 sec in buffer (50 mM Tris, pH 7.4), centrifugate at 43.000 x g for 10 min (Sigma 3K30), suspense the membrane preparation in the buffer mentioned above, store the aliquots at -80 °C.

Binding protocol: incubate CHO-hA_1 membrane preparation (50 µg protein content) in incubation buffer (50 mM Tris, 3 U/mL adenosine deaminase, pH 7.4), 10 nM [^{3}H]CCPA (2-chloro-N^6-cyclopenthyl-adenosine) (80.000 dpm) and 10 µM R-PIA (N^6-[L-2-phenylisopropyl]adenosine) to define the non-specific binding or test compound in a total volume of 100 µL for 3 hr at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked in 0.5% polyethylenimine for 3 hours), wash 4x with 1 mL ice-cold 50 mM Tris (pH 7.4) on 96-well Brandel Cell Harvester. Detection of activity: in 96-well plate in the presence of HiSafe-3 coctail in beta-counter (1450 Microbeta, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Human adenosine A_{2a} receptor binding

Binding protocol: incubate 7 µg of membranes (human A_{2a} adenosine receptors transfected into HEK-293 cells, source: Receptor Biology, Inc.), buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EDTA, 2 U/mL adenosine deaminase, pH 7.4), 20 nM [^{3}H]CGS-21680 (2-[*p*-(2-carbonylethyl)phenylethylamino]-5`-N-ethylcarboxamido-adenosine) (200.000 dpm) and 50 µM NECA (5`-N-ethylcarboxamido-adenosine) to define the non-specific binding or test compound in a total volume of 100 µl for 90 min at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked in 0.5% polyethylenimine), wash 4x with 1 mL ice-cold 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, 0.9 % NaCl, pH 7.4) on 96-well Brandel Cell Harvester. Detection of activity: in 96-well plate in the presence of HiSafe-3 coctail in beta-counter (1450 Microbeta, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Human adenosine A_{2b} receptor binding

Binding protocol: incubate 20.8 μg of membranes (human A_{2b} adenosine receptors transfected into HEK-293 cells, source: Receptor Biology, Inc.), buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.1 mM benzamidine, 2 U/mL adenosine deaminase, pH 6.5), 32.4 nM [^{3}H]DPCPX (8-cyclopenthyl-1,3-dipropylxanthine) (800.000 dpm) and 100 μM NECA (5`-N-ethylcarboxamido-adenosine) to define non-specific binding or test compound in a total volume of 100 μL for 30 min at room temperature. Filter over Whatman GF/C glass fibre filters (presoaked in 0.5% polyethylenimine), wash 4x with 1 mL ice-50 mM Tris-HCl (pH 6.5) on 96-well Brandel Cell Harvester. Detection of activity: in 96-well plate in the presence of HiSafe-3 coctail in beta-counter (1450 Microbeta, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Results

We consider the compounds as biologically active ones if they inhibit the binding of the radioligand on human adenosine A_3 receptors with an activity above 80 % at 1 μM in our experimental conditions.

The dissociation constant (K_d) of [^{125}I]AB-MECA on CHO-hA_3 membrane preparation is determined by isotope saturation studies with the help of Scatchard analysis (G. Scatchard, Ann. N. Y. Acad. Sci. 51:660, 1949). The IC_{50} is converted to an affinity constant (K_i) by application of the Cheng-Prusoff equation (Y. J. Cheng and W. H. Prusoff, Biochem. Pharmacol. 22:3099, 1973).

Several compounds of the general formula (I), (II), (III) and (IV) display remarkable biological effects. The compounds of the general formula (IA), defined in claim 2, as a subgroup of the general formula (I), defined in claim 1, exert the most important activities. Except of 5 compounds, their K_i values are not higher than 20 nM. The compounds given as examples are especially advantageous. Their K_i values in human adenosine A_3 receptor binding studies are between 0.19 and 0.69 nM. The K_i values of the most advantageous compounds are 0.14 and 0.15 nM.

The compounds possess proper bioviabilities and exert at least 10,000-fold selectivity in respect of human adenosine A_1, A_{2a} and A_{2b} receptor subtypes.

Further, the duration of their action at intravenous and oral administration is long enough, their ED_{50} values are low, their toxicological and side-effect profiles are advantageous.

Data above make the compounds of the general formula (I) probable for therapeutic applications.

Claims

1) Compounds of the general formula (I) - wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

X stands for a $-CH_2-$ group, -NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

2) Compounds of the general formula (IA) according to claim 1 - wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group. or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted with a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

3) Compounds of the formula (IA) according to claim 2, -wherein

R^1 stands for hydrogen atom or a methyl group;

R^2 stands for hydrogen atom or a methyl group;

R^3 stands for phenyl group, thienyl group or furyl group;

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or cyano group;

R^7 stands for 4-methoxyphenyl group, 3-methylphenyl group, 3-thienyl group or 3-furyl group;

X stands for –NH- group or oxygen atom and

n stands for 1-

and their salts, solvates and optically active isomers and their salts and solvates.

4) Compounds according to claims 1-3 as follows:

3-Methyl-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

4-Methoxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3-Methoxy- N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

N-(4-benzylamino-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

4-Methoxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)furan-2-carboxamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)thiophene-2-carboxamide

and their salts, solvates, optically active isomers and their salts and solvates.

5) Process for the preparation of a compound of the general formula (I), its salts, solvates, optically active isomers and their salts and solvates-wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1, characterized

by selective hydrolysis of a bis acid amide of the general formula (II) -wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1- and if desired transforming the substituens of the compound of the general formula (I) thus obtained in each other by methods known per se and/or transforming the compound of the general formula (I) thus obtained into its salts, or solvates, or liberating it from its salts or solvates and/or separating it into its optically active isomeric forms or transforming the optically active forms into the racemic form

6) Process according to claim 5, characterized by carrying out the selective hydrolysis in an alcoholic medium in the presence of an alkali hydroxide, preferable potassium or sodium hydroxide

7) Pharmaceutical compositions containing as active ingredient one or more compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry.

8) Pharmaceutical compositions according to claim 7 containing as active ingredient one or more compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry

9) Pharmaceutical composition according to claim 8 containing as active ingredient one or more compound of claim 4.

10)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - in the treatment of diseases in development of which the receptor A_3 plays a role.

11)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claim 10 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition of the protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of intraocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

12) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claims 10 and 11 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison's disease, Crohn's disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes as active ingredient.

13) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – according to claims 10, 11 and 12 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrhytmia and renal diseases as active ingredient.

14) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - in the treatment of diseases in development of which the receptor A_3 plays a role.

15) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11},R^{12}, X and n have the same meaning as defined in claim 2 - according to claim 13 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition or protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of the inraocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

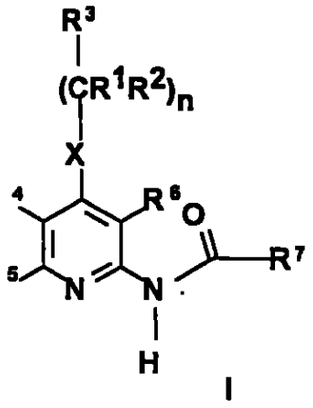
16) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - according to claims 13 and 14 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison's disease, Crohn's disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes as active ingredient.

17) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – according to claims 14, 15 and 16 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic reactions, inflammatory diseases, ischemia, hypoxia, arrhytmia and renal diseases.

18) Compounds of the general formula (II)- wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1.

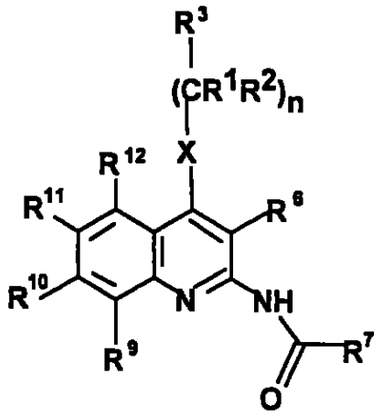
19) Compounds of the general formula (III)-wherein R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n have the same meaning as defined in claim 1, with the proviso that R^3 cannot stand for phenyl group, if R^1 and R^2 stand for hydrogenatom, n=1, X stands for a –NH– group, R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano group.

20) Compounds of the general formula (IV)- wherein R^4, R^5, and R^6 have the same meaning as defined in claim 1.



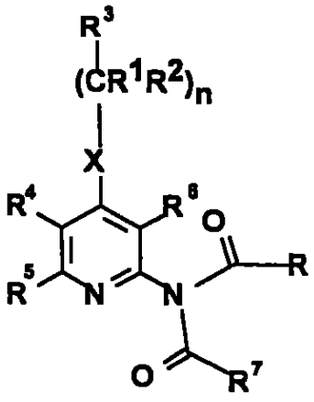
I

Figure 1



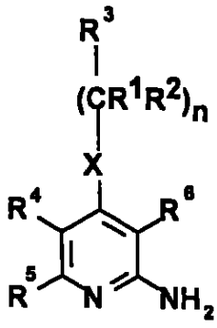
IA

Figure 2



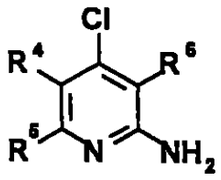
II.

Figure 3



III.

Figure 4

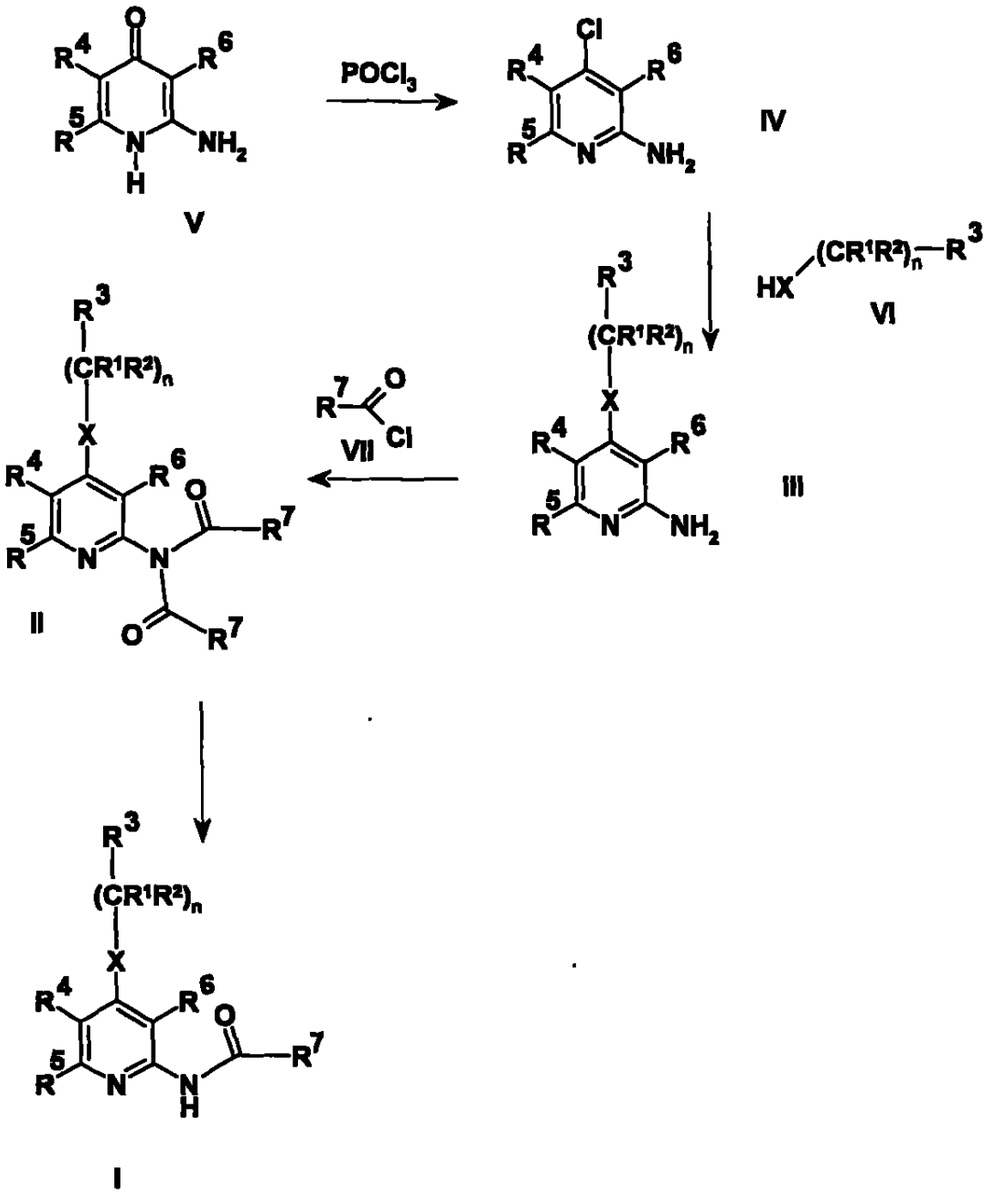


IV

Figure 5

Figure 6

Reaction scheme 1.



56

2002 OKT 07

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

444 1/200

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

10/07

To:
SANOFI-SYNTHELABO
Attn. Mihályi, György
To u. 1-5.
H-Budapest 1045
HUNGARY

Date of mailing *(day/month/year)* 07/10/2002	
Applicant's or agent's file reference Case 881/PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/HU 02/ 00048	International filing date *(day/month/year)* 29/05/2002
Applicant SANOFI-SYNTHELABO	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Margarita Tzelepi

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
Case 881/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU 02/00048	29/05/2002	31/05/2001
Applicant		
SANOFI-SYNTHELABO		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   AMINOQUINOLINE AND AMINOPYRIDINE DERIVATIVES AND THEIR USE AS ADENOSINE A3 LIGANDS

5. With regard to the abstract,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. ____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

60

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CENTRAL UNIT RECEIVING SECTION

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Group PCTISA

Sent by : Margarita Tzelepi

Date request : 25/09/2002

61

International application No.
PCT/HU 02/00048

INTERNATIONAL SEARCH REPORT

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

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

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

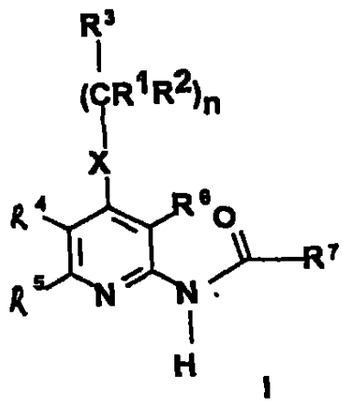
[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 02/00048

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

Compounds of the general formula I



I

wherein R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; are strong adenosine A_3 receptor ligands preferably antagonists.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00048

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/48 A61K31/4706 A61P43/00 C07D405/12 C07D409/12
C07D409/14 C07D405/14 C07D215/46 C07D401/12 C07D213/85

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992 (1992-06-22) Columbus, Ohio, US; abstract no. 255453f, GEWALD K. ET AL.: "Simple synthesis of 2,3-diaminoquinoline-3-carbonitriles." XP002214323 abstract & J. PRAKT. CHEM/CHEM.-ZTG., vol. 334, no. 1, - 1992 pages 89-91, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1992:255453 XP002214325 compound with RN 141648-22-8	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2002	07/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00048

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 11244 A (ZENECA LTD.) 27 April 1995 (1995-04-27) * page 110-111: example 87a) and 82b) *	1
P,X	CHEMICAL ABSTRACTS, vol. 136, Columbus, Ohio, US; abstract no. 69693x, SARHAN, ABD EL-WARETH A. O. ET AL.: "Synthesis, characterization and reactions of 2-deoxo-5-deazaalloxazines." XP002214324 abstract & BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 11, - 2001 pages 2993-2998, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 2001:845787 XP002214326 compounds with RN 383866-39-5 and -61-3	1
A	EP 1 180 518 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 20 February 2002 (2002-02-20) page 5	1,7

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 02/00048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511244 A	27-04-1995	AT 198072 T	15-12-2000
		AU 721139 B2	22-06-2000
		AU 6899998 A	30-07-1998
		AU 688393 B2	12-03-1998
		AU 7944094 A	08-05-1995
		CA 2171332 A1	27-04-1995
		CN 1138332 A ,B	18-12-1996
		CZ 9601138 A3	11-09-1996
		DE 69426422 D1	18-01-2001
		DE 69426422 T2	10-05-2001
		DK 724583 T3	05-03-2001
		EP 1004582 A2	31-05-2000
		EP 0724583 A1	07-08-1996
		ES 2154686 T3	16-04-2001
		FI 961696 A	18-04-1996
		FI 970907 A	03-03-1997
		WO 9511244 A1	27-04-1995
		HU 74161 A2	28-11-1996
		JP 9504519 T	06-05-1997
		KR 261209 B1	01-09-2000
		NO 961584 A	19-04-1996
		NZ 275472 A	25-03-1998
		NZ 329303 A	28-01-2000
		PL 314041 A1	05-08-1996
		PT 724583 T	30-03-2001
		RU 2168511 C2	10-06-2001
		SG 59971 A1	22-02-1999
		SI 724583 T1	30-04-2001
		SK 50496 A3	05-03-1997
		TW 406082 B	21-09-2000
		US 6232313 B1	15-05-2001
		US 6103721 A	15-08-2000
		US 5744471 A	28-04-1998
		ZA 9408178 A	24-04-1995
EP 1180518 A	20-02-2002	AU 3840100 A	10-11-2000
		BR 0009952 A	26-03-2002
		EP 1180518 A1	20-02-2002
		NO 20015156 A	18-12-2001
		CN 1353710 T	12-06-2002
		CZ 20013805 A3	17-04-2002
		WO 0064894 A1	02-11-2000
		JP 2001114779 A	24-04-2001

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ European Patent Office

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: Case 881/PCT

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/HU2/00048	29 May 2002 (29.05.2002)	31 May 2001 (31.05.2001)

Title of invention: NEW COMPOUNDS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SANOFI-SYNTHELABO
174, avenue de France
F-75013 Paris
FRANCE

Telephone No.: +33 1 41 24 12 37
Facsimile No.: +33 1 41 24 12 66
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
FRANCE	FRANCE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ARÁNYI, Péter
Budapest, Bimbó út 216.
H-1026 Hungary

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BALÁZS, László
Dunakeszi, Madách u. 15.
H-2120 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2.

International application No.
PCT/HU2/00048

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BALOGH, Mária
Dunakeszi, Barátság u. 21.
H-2120 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BATA, Imre
Budapest, Frankel Leó u. 7.
H-1027 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BÁTORI, Sándor
Budapest, Rákóczi F. u. 268/A
H-1214 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

T.NAGY, Lajos
Budapest, István u. 47. II/14.
H-1078 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

☒ Further applicants are indicated on another continuation sheet.

Sheet No. .3.

International application No.
PCT/HU2/00048

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TÍMÁRI, Géza
Vecsés, Zöldfa u. 8.
H-2220 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOÉR, Kinga
Budapest, Vízimolnár u. 2.
H-1031 HUNGARY

Sheet No. .3.

International application No.
PCT/HU2/00048

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TÍMÁRI, Géza
Vecsés, Zöldfa u. 8.
H-2220 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOÉR, Kinga
Budapest, Vízimolnár u. 2.
H-1031 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

FINANCE, Olivier
9, rue de Nazareth, Bat D
F-34090 Montpellier
FRANCE

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
FRANCE	FRANCE

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KAPUI, Zoltán
Budapest, Etele út 56/a
H-1115 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

☒ Further applicants are indicated on another continuation sheet.

Sheet No. 4.

International application No.
PCT/HU2/00048

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MIKUS, Endre
Budapest, Ida u. 96.
H-1162 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SZAMOSVÖLGYI, Zsuzsanna
Budapest, Bajnok u. 7.
H-1063 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SZELECZKY, Gábor
Budapest, Ivánka Pál u. 30.
H-1155 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

URBÁN-SZABÓ, Katalin
Budapest, Szent László u. 158.
H-1131 HUNGARY

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
HUNGARY	HUNGARY

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 5

International application No.
PCT/HU2/00048

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SANOFI-SYNTHELABO, c/o
Dr. György Mihályi and Katalin Mármarosi
Budapest, Tó u. 1-5.
H-1045 HUNGARY

Telephone No.
+36 1 369 5706

Facsimile No.
+36 1 272 0727

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description
☐ as originally filed
☐ as amended under Article 34

the claims
☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☐ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

71 72

Sheet No. .6.

International application No.
PCT/HU2/00048

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☒ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☒ other *(specify)*: Transmittal Letter

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Budapest, 15 November 2002

For and on behalf of SANOFI-SYNTHELABO

Dr. György Mihályi

Katalin Mármarosi

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

3478/03

2003 AUG 22

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Mihályi, György
SANOFI-SYNTHELABO
To u. 1-5.
H-Budapest 1045
HONGRIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.08.2003
Applicant's or agent's file reference: Case 681/PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU02/00048	29.05.2002	31.05.2001

Applicant
SANOFI-SYNTHELABO

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vetter-Dejongh, M-H Tel. +49 89 2399-8516

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

2003 OKT 28

From the INTERNATIONAL BUREAU

PCT

COMMUNICATION IN CASES FOR WHICH NO OTHER FORM IS APPLICABLE

To:

MIHÁLYI, György
Sanofi-Synthelabo
Tó u. 1-5
H-1045 Budapest
HONGRIE

Date of mailing (*day/month/year*) 15 October 2003 (15.10.03)	
Applicant's or agent's file reference Case 881/PCT	REPLY DUE see paragraph 1 below
International application No. PCT/HU02/00048	International filing date (*day/month/year*) 29 May 2002 (29.05.02)
Applicant SANOFI-SYNTHELABO	

1. ☐ REPLY DUE within _____ months/days from the above date of mailing

☐ NO REPLY DUE, however, see below

☒ IMPORTANT COMMUNICATION

☐ INFORMATION ONLY

2. COMMUNICATION:

The International Bureau informs the applicant that due to a clerical error the two sheets of drawings for the above-mentioned international application have not been published with the pamphlet on 05 December 2002.

A new publication will take place on 13 November 2003.

The International Bureau regrets any inconvenience that this error may have caused.

A copy of this notification is being sent to the receiving Office, and the designated Offices.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Catherine MASSETTI (Fax 338-87-20)
Facsimile No.	Telephone No.

Form PCT/IB/345 (July 1992)

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Mihályi, György
SANOFI-SYNTHELABO
To u. 1-5.
H-Budapest 1045
HONGRIE

04/29 → osi → ME

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	23.04.2003
Applicant's or agent's file reference	Case 881/PCT
REPLY DUE	within 3 month(s) from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/HU02/00048	29/05/2002	31/05/2001

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

C07D215/48

Applicant

SANOFI-SYNTHELABO

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/09/2003.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Stix-Malaun, E

Formalities officer (incl. extension of time limits)
Vollmann, V
Telephone No. +49 89 2399 7278

WRITTEN OPINION International application No. PCT/HU02/00048

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

   Description, pages:

   1-42 as originally filed

   Claims, No.:

   1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-17 (Industrial Applicability),

because:

   ☒ the said international application, or the said claims Nos. 10-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,5,7,19,20 no,10-18 yes
Inventive step (IS)	Claims	1-20 no
Industrial applicability (IA)	Claims	1-9,18-20 yes

2. Citations and explanations
see separate sheet

III NON-ESTABLISHMENT

Claims 10-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992 (1992-06-22) Columbus, Ohio, US; abstract no. 255453f, GEWALD K. ET AL.: 'Simple synthesis of 2,3-diaminoquinoline-3-carbonitriles.' XP002214323 & J. PRAKT. CHEM/CHEM.-ZTG., vol. 334, no. 1, - 1992 pages 89-91, -& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1992:255453 XP002214325

D2: WO 95 11244 A (ZENECA LTD.) 27 April 1995 (1995-04-27)

D3: CHEMICAL ABSTRACTS, vol. 136, Columbus, Ohio, US; abstract no. 69693x, SARHAN, ABD EL-WARETH A. O. ET AL.: 'Synthesis, characterization and reactions of 2-deoxo-5-deazaalloxazines.' XP002214324 & BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 11, - 2001 pages 2993-2998, -& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 2001:845787 XP002214326

D4: EP-A-1 180 518 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 20 February 2002 (2002-02-20)

D5: Beistein abstract (containing BRN3690429 & Chem.Ber.,64,1931,21,26)

have been considered for the examination procedure.

D3 might become relevant prior art in the european phase.
D5 was not cited in the international search report. A copy of the document is appended hereto.

2. NOVELTY

The subject-matter of the claims is anticipated by D1,D2,D5 (Article 33(2) PCT) (see abstract D1). D1 discloses exemplified compounds which are covered by present formula (III).D2 discloses a generic expression (see p. 148,scheme 6) which forms an overlapping part with present formulae (I),(IA). It comprises additionally compounds which fall within the said overlap (see p. 110-110, examples 82a,b,D2).
The compound of D5 (see Beilstein Registry Number 3690429) is cited exemplary for countless novelty destroying compounds which fall under formula (IV) of claim 20.
Accordingly the presently claimed subject matter lacks novelty.

The compounds of D4 lack the linker X.

Exemplified compounds and claims which are directed to second medical indication appear to be novel.

3. INVENTIVE STEP

The presently claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons:

(a)The problem of the present application may be seen in the provision of further pyridine derivatives which are useful as adenosine receptor ligands which show antagonistic effects and high selectivity for the A3 receptor and are therefore useful in the treatment of inflammatory diseases.

The closest state of the art for the present application is represented by D4.

The compounds of D4 are useful in the same pharmaceutical field as the present ones.
As already sated under item novelty the presently claimed compounds lack the linking group X. X may represent inter alia CH2. The examples of D4 show the same selection as the present ones (see tables 1-6,p.59-64) and differ therefore in a methylene unit,only.

Thus,the present compounds can be seen as simply analogous to those of D4. It is therefore obvious for the skilled person to assume that the presently claimed compounds show the alleged activity.

The problem defined under item (a) has been solved in an obvious manner.

(b) Therefore the problem of the present application has to be seen in the provision of a novel process which exhibits unexpected effects in relation to the compounds of D4.

Apart from a general description from test procedures, no such effects or properties are indicated in the application.

Accordingly,no solution has been provided to the problem as defined under item (b).
An inventive contribution is not detectable with respect to the process or the intermediates. In addition to that it appears that the compounds according to formula (IV) do not contain the essential technical feature.

Accordingly inventive step cannot be acknowledged.

3. INDUSTRIAL APPLICABILITY

For the assessment of the present Claims 10-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of

claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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Our ref: **Case 881 PCT**
Date: 27 May 2003
K. Mármarosiné/CsI

Dear Sirs,

Re: International Application No PCT/HU02/00048, written opinion mailed on 23.04.2003.

Reverting to the Written opinion mailed on 23.04.2003, please find enclosed the amended set of claim (Enclosure 1), together with page 8 of the amended specification (Enclosure 2). We also enclose one full copy of the amended version of our application (Enclosure 3).

Amendments have been made to overcome the objections raised in the written opinion.

NOVELTY

Compounds of the general formula III described in the cited prior arts D1 and D2 are excluded from the scope of amended claim 19 „with the further proviso that R^3 cannot stand for hydrogenatom, methyl, ethyl, 4-methoxyphenyl or cyclohexyl group, if n=0, X stands for a $-NR^8$ - group, R^8 stands for hydrogenatom or methyl group R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano group, and with the further proviso that R^3 cannot stand for hydrogenatom, if, n=0, X stands for a $-CH_2-$ group, R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano or amino-carbonyl group."

Compound of the general formula IV described in the prior art D5 is excluded from the scope of amended claim 20 „with the proviso that R^6 cannot stand for hydrogenatom, if R^4 stands for hydrogenatom and R^5 stands for a 4-halogenatom."

83

84

Compounds described in the cited prior art D2 do not constitute a novelty distroying material as neither the compounds of the generic expression on page 148, scheme 6, nor those of examples 82a and 82b contain an –NH-group between the carbon atom in position 3 of the quinolin ring and the CO-group of the side chain.

With the aforesaid limitations the amended claims do fulfil the requirements of Article 33(2)PCT.

INVENTIVE STEP

Compounds described in D4 cited as the closest state of the art are entirely different from the compounds claimed in the present application as not only the linking group X lacks, but also group Z is different. Group Z in D4 stands for a bond or a divalent acyclic hydrocarbon, whereas according to general formula I of the present application it must be a CO-group.

Thus the compounds of the present application cannot be seem as simply analogous to those of D4.
Moreever although it is true that compounds of D4 poccess A3 antagonist effect, but the only IC_{50} value given in the specification is 11,6 nM, whereas the compounds of the present application are effective in 0,19-0,65 nM. The Ki values of the most advantageous compounds are 0,14 and 0,15 nM.
According to the aforesaid the amended claims do fulfil the requirements of Article 33(3)PCT.

Please establish the IPER on the basis of above facts.

Yours very truly,

.....	.....
Dr. György Mihályi Director of Corporate and Legal Affairs	Katalin Mármarosi Industrial Property Rights Manager

Enclosures: 1, 2 and 3

PATENT COOPERATION TREATY

2003 JAN 02

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Mihályi, György
SANOFI-SYNTHELABO
To u. 1-5.
H-Budapest 1045
HONGRIE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	23/12/2002
Applicant's or agent's file reference: Casa 381/PCT	REPLY DUE within 2 / 00 months/days from the above date of mailing
International application No.: PCT/HU 02/ 00048	International filing date *(day/month/year)*: 29/05/2002
Priority date *(day/month/year)*: 31/05/2001	
International Patent Classification (IPC) or both national classification and IPC: C07D215/48	
Applicant: SANOFI-SYNTHELABO	

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/09/2003.

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Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
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Form PCT/IPEA/408 (cover sheet) (march 2002)

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

DERIVADOS DE AMINOQUINOLINA Y AMINOPIRIDINA Y SU USO COMO LIGANDOS A3 ADENOSINA

La presente invención se relaciona con ligandos del recepto A_3 de adenosina de la fórmula general (I), dentro de aquellos preferiblemente antagonistas, así como también su sales, solvatos e isómeros, y las composiciones farmacéuticas que los contienen, con el uso de los compuestos de la fórmula general (I), así como también sus sales, solvatos e isómeros, con la preparación de los compuestos de la fórmula general (I) y sus sales, solvatos e isómeros, adicionalmente con intermedios nuevos de las fórmulas generales (II) (III) y (IV) y con la preparación de estos.

La adenosina es un componente bien conocido de varias moléculas endógenas (ATP,NAD^+, ácido nucleico). Además, esta juega un papel regulatorio importante en muchos procesos fisiológicos. El efecto de la adenosina sobre la función cardiaca fue descubierto alrededor de 1929. (Dury y Szentgyörgyi, J Physiol 68:213, 1929). La identificación de un número creciente de funciones fisiológicas mediadas por adenosina y el descubrimiento

87

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de nuevos subtipos receptores de adenosina dan posibilidades para aplicación terapéutica de ligandos especificos (Poulse, S:A: y Quinn, R.J. Bioorganic and Medicinal Chemistry 6:619, 1998).

A la fecha, los receptores para adenosina se han clasificado en tres clases importantes: A_1, A_2 y A_3. el subtipo A_1 es parcialmente responsable de inhibir la adelinata ciclasa al acoplar una proteina de membrana G_i, influencia parcialmente otros segundos sistemas de mensajeros. El subtipo receptor A_2 se puede subdividir en dos subtipos adicionales -A_{2a} y A_{2b} -, cuyos receptores estimulan la actividad de adenilato ciclasa. Las secuencias de los receptores de A_3 adenosina han sido recientemente identificados en biblioteca cDNA de testiculo de rata. Posteriormente se probó que este corresponde a un receptor de adenosina funcional nuevo. La activación de los receptores A_3 está conectada también con varios sistemas mensajeros segundos: inhibición del adenilato ciclasa, estimulación de la fosfolipasa C y D.

Los receptores de adenosina son encontrados en varios órganos y regulan sus funciones. Tanto los receptores A_1 como A_{2a} juegan papeles importantes n el

sistema nervioso central y sistema cardiovascular. En el CNS, la adenosina inhide la liberación de transmisores sinápticos cuyo efecto es mediado por receptores A_1. en el corazón, también los receptores A_1 median los efectos inotropticos, cronotropticos y dromotropicos negativos de la adenosina. Los receptores A_2 de adenosina localizados relativamente en cantidades más altas en el striatum, muestran interacción funcional con receptores de dopamina en la regulación de transmisión sinóptica. Los receptores de adenosina A_{2a} sobre las células musculares endoteliales y suaves son responsables de la vasodilatación inducida por adenosina.

Sobre la base de identificación de mARN, los receptores de adenosina A_{2b} son ampliamente distribuidos en diferentes tejidos. Ellos se han identificado casi en cada tipo de célula, pero su expresión es la más alta del intestino y en la vejiga. Es subtipo probablemente tiene también importante función regulatoria en la regulación del tono vascular y juega un papel importante en la función de las células mástil.

Contrario a los receptores A_1 y A_{2a}, donde la distribución de tejidos se detectó sobre el nivel de

89

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proteína, la presencia de los receptores A_{2b} y A_3 se detectó sobre la base de su nivel mARN. Los niveles de expresión para receptores de adenosina A_3 son por el contrario bajos comparados con otros subtipos y altamente dependientes de las especies. Los receptores de adenosina A_3 son expresados primariamente en el sistema nervioso central, los testículos, el sistema inmune y parecen estar involucrados en la modulación de la liberación mediadora de células mástil en la reacción hipersensitiva inmediata.

Los antagonistas A_3 publicados hasta ahora en la literatura pertenecen a los grupos de flavonoides, derivados de 1,4-dihidropiridina, trizoloquinazolinas, tiazolonaftiridinas y tiazolopirimidinas. La presente invención se relaciona con un tipo novedoso de antagonista A_3 efectivo, que tiene la estructura aminoquilonina.

Para uso terapéutico es esencial asegurar que la molécula no se una, o se una solamente en el caso de una concentración muy alta a los subtipos A_1, A_{2a} y A_{2b} del receptor de adenosina. Nuestra presente invención se relaciona con los compuestos de la fórmula general (I)

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así como también sus sales, solvatos e isómeros que tienen gran selectividad para el subtipo A_3 del receptor de adenosina.

Nuestro objetivo fue preparar ligandos A_3 primero que todo con la estructura quinolina, y dentro de aquellos preferiblemente antagonistas, que tienen un fuerte efecto antagonista y muestran alta selectividad para el receptor A_3, es decir, ellos inhiben el recepto A_3 en mucha menor concentración que lo que ellos inhiben los receptores A_1, A_{2a} y A_{2b}. Objetivos adicionales fueron tener estabilidad, biodisponibilidad, índice terapéutico y datos de toxicidad que hagan posible el desarrollo de nuevos compuestos en sustancias de droga y que debido a su absorción enteral favorable los compuestos se pueden aplicar oralmente.

Hemos encontrado que los compuestos de la fórmula general (I)- en donde

R^1 representa átomo de hidrogeno o grupo alquilo C_{1-4} recto o ramificado;

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92

R^2 representa átomo de hidrogeno o grupo alquilo C_{1-4} recto o ramificado;

R^3 representa átomo de hidrogeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante uno o más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno, o para un anillo heteroaromático de 5 o 6 miembros que contienen uno, dos o tres átomos de nitrógeno o un átomo de hidrogeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre-

Opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos alcoxi C_{1-4} rectos o ramificados, o átomo de halógeno; R^4 y R^5 representa átomos de hidrogeno o forma junto con el grupo 1,3-butadienilo, opcionalmente sustituido mediante un grupo metilenedioxi o uno más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi o átomo de halógeno;

R^6 representa átomo de hidrogeno o grupo ciano, un grupo aminocarbonilo, un grupo alcoxicarbonilo C_{1-4} o un grupo a carboxi;

R^7 representa átomo de hidrogeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo benzilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante un grupos metilenedioxi o uno o más grupos alquilo C_{1-4} recto o ramificado, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi, grupo difluorometilo, grupo ciano o átomo de halógeno, o para un anillo heteroaromático de 5 o 6 miembros - que contienen uno, dos o tres átomos de nitrógeno o un átomo de hidrogeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre-

Opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos alcoxis C_{1-4} rectos o ramificados, o átomo de halógeno,

X representa un grupo $-CH_2-$, grupo -NH-, grupo $-NR^8-$, o un atomo de azufre o un átomo de oxígeno o un grupo sulfo o un grupo sulfoxi- en donde R^8 representa un grupo alquilo C_{1-4} recto o ramificado o un grupo cicloalquilo C_{3-6} -;

93

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n representa cero, 1 o 2- y su sales, solvatos e isómeros y las sales , solvatos de los últimos, llenan los criterios anteriores.

Los significados detallados de los sustituyentes anteriormente listados son como sigue:

Mediante un grupo alquilo C_{1-4} recto o ramificado nosotros significamos metilo-, etilo-, propilo-,isopropilo-,butilo-, isobutilo-, butilo secundario-, butilo terciario-, preferiblemente etilo- o grupo metilo.

Mediante un grupo alcoxi C_{1-4} recto o ramificado nosotros significamos metoxi-, etoxi-, propoxi-,isopropoxi-,butoxi-, isobutoxi-, butoxi secundario-, butoxi terciario-, preferiblemente etoxi- o grupo metoxi.

Mediante un grupo cicloalquilo C_{3-6} nosotros significamos ciclopropil-, ciclobutil-, ciclopentil- o el grupo ciclohexilo.

Mediante el grupo 1,3-butadienil- nosotros significamos un grupo (-CH=CH-CH=CH-) es decir el anillo

94/95

de piridina sustituido mediante los sustituyente R^4 y R^5 significan un anillo de benzopiridina o mediante su nombre trivial un anillo de quinolina.

El anillo heteroaromático que contiene uno o dos o tres átomos de nitrógeno significan pirrol, imidazol, pirazol, 1,2,3-triazol, 1,2,4-triazol, piridina, pirimidina, piridazina, pirazina y 1,3,4-triazina. El anillo es opcionalmente sustituido mediante alquilo C_{1-4}, o grupo alcoxi o mediante un átomo de halógeno.

El anillo heteroaromático que contiene uno átomo de nitrógeno y un átomo de oxígeno o azufre significa el oxazol, isoxazol, tiazol o anillo de isotiazol. El anillo es opcionalmente sustituido mediante alquilo C_{1-4}, o grupo alcoxi o mediante un átomo de halógeno.

Las sales y los compuestos de fórmula general (I) significan sales dadas con ácidos y bases inorgánicas u orgánicas. Las sales preferidas son aquellas dadas con ácidos farmacéuticamente aceptados como por ejemplo ácido clorhídrico, ácido sulfúrico, ácido etanosulfónico, ácido tartárico, ácido succínico, ácido fumárico, ácido málico,

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ácido cítrico, y bases, como por ejemplo hidróxido de sodio, hidróxido de potasio, etanolamina.

Los sulfatos significan solvatos dados con varios solventes, como por ejemplo con agua o etanol.

Los compuestos para la fórmula general (I) muestran isómeros geométricos y ópticos, por lo tanto la invención también se relaciona con mezclas de los isómeros geométricos, con isómeros geométricos racémicos u óptimamente activos, así como también con sus sales y solvatos.

Un grupo favorable de los compuestos de la fórmula general (I) es el formado por los compuestos de la fórmula general (IA), en donde

R^1 representa átomo de hidrogeno o un grupo alquilo C_{1-4} recto o ramificado;

R^2 representa átomo de hidrogeno o un grupo alquilo C_{1-4} recto o ramificado;

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R^3 representa átomo de hidrogeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo tienilo, grupo furilo, opcionalmente sustituido mediante un o más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno, o por anillo heteraromático de 5 o 6 miembros que contiene uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre- opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno;

R^9, R^{10}, R^{11} y R^{12} independientemente significan átomo de hidrogeno o grupo alquilo C_{1-4} recto o ramificado, o grupo alcoxi C_{1-4} recto o ramificado, o grupo hidroxi o átomo de halógeno, o

R^9, y R^{12} representan átomo de hidrogeno y R^{10} y R^{11} forman juntos un grupo metilenedioxi;

R^6 representan átomo de hidrogeno o grupo ciano, grupo aminocarbonilo, grupo alcoxicarbonilo C_{1-4}, o grupo carboxi;

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R^7 representan átomo de hidrogeno o grupo alquilo C_{1-4} recto o ramificado, un grupo fenilo, grupo benzilo, grupo tienilo, grupo furilo, opcionalmente sustituido mediante un grupo metilenedioxi, o uno o más grupos alquilo C_{1-4} recto o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o un anillo heteroaromático de 5 6 miembros que contiene uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre- opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno,

X representa un grupo $-CH_2-$,grupo -NH-, grupo $-NR^8-$, o un átomo de azufre o un átomo de oxígeno o un grupo sulfo o un grupo sulfoxi- en donde R^8 representa un grupo alquilo C_{1-4} recto o ramificado o un grupo cicloalquilo C_{3-6}-;

n representa cero, 1 o 2- y su sales, solvatos e isómeros óptimamente activos y las sales , solvatos de estos

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Un grupo favorable de los compuestos de la fórmula general (IA) es el formado por los compuestos en donde

R^1 representa átomo de hidrogeno, o un grupo metilo;

R^2 representa átomo de hidrogeno, o un grupo metilo;

R^3 representa grupo fenil- o tienil- o furilo;

R^9, R^{10}, R^{11}, y R^{12} independientemente significan átomo de hidrogeno o grupo alquilo C_{1-4} recto o ramificado, o grupo alcoxi C_{1-4} recto o ramificado, o grupo hidroxi o átomo de halógeno, o

R^9, y R^{12} representan átomo de hidrogeno y R^{10} y R^{11} forman juntos un grupo metilenedioxi;

R^6 representan átomo de hidrogeno, o grupo ciano;

R^7 representan 4-metoxifenil-, 3-metifenil-, 3-metoxifenil-, 3-tienil-, o el grupo 3-furil-,

X representa un grupo -NH-, o átomo de oxígeno

n representa 1-

y sus sales, sulfatos, isómeros óptimamente activo y las sales, solvatos de estos.

Especialmente favorable son los compuestos siguientes que cumplen con los criterios anteriores:

3-metil-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida;

4-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida;

3-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida;

3,4-metilenedioxi-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida;

N-(4-benzilamino-3-cianoquinolin-2-il) tiofeno-2-carboxamida;

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101

N-(4[2-tienilmetilamino] -3-cianoquinolin-2-il) tiofeno-3-carboxamida;

4-metoxi-N-(4-[2- tienilmetilamino] -3-cianoquinolin-2-il) benzamida;

3,4-metilenedioxi-N-(4-[2- tienilmetilamino] -3-cianoquinolin-2-il) benzamida;

N-(4[2-furilmetilamino]-3-cianoquinolin-2-il) furan-2-carboxamida;

N-(4[2-furilmetilamino]-3-cianoquinolin-2-il) tiofeno-3-carboxamida,

Y sus sales, solvatos, isómeros óptimamente activos y sus sales, solvatos de estos.

De acuerdo con otro de sus aspectos, la presente invención también se relaciona con composiciones farmacéuticas que contienen los principios activos de los compuestos de fórmula general (I) o sus isómeros, sales y solvatos, que son preferiblemente composiciones orales pero inhalable, formulaciones parenterales y

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102

transdérmicas también son sujeto de la invención. Las composiciones farmacéuticas anteriores pueden ser sólidas o liquidas, tales tabletas, glóbulos, cápsulas, parches, soluciones, suspensiones o emulsiones. Las composiciones sólidas, primero que todas las tabletas y cápsulas son formas farmacéuticamente preferidas.

Las composiciones farmacéuticas anteriores son preparadas al aplicar excipientes farmacéuticos usuales y al utilizar métodos estándar.

Los compuestos de la fórmula general (I), se pueden utilizar en patología de tratamiento, en el desarrollo de los cuales el receptor A_3 juega un papel.

Los compuestos de la presente invención que tienen actividad selectiva del receptor A_3 se puede utilizar en el tratamiento terapéutico y/o preventivo y disfunciones del corazón, riñón, sistema respiratorio, sistema nervioso central. Ellos inhiben el efecto protector de la adenosina en el crecimiento de células tumorales, evitan la desgranulación de las células mástil, inhiben la producción de citoquina, reduce la presión intraocular,

inhiben la liberación de TNFα, inhibe la migración de eosinófilos, neutrófilos y otras células inmune, inhiben la broncoconstricción y la extravasación de plasma.

Con base en estos efectos, los antagonistas del receptor A3 de adenosina de la presente invención se puede utilizar terapéuticamente como antiinflamatorios, antiasmático, antiisquémicos, antidepresivos, antiarritmicos, protectores reales, antitumorales, drogas antiparquinson y mejoramiento cognitivo. También ellas pueden ser útiles en el tratamiento o prevención de daño por repercusión de miocardio, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de desetres respiratorio (ARDS) incluyendo bronquitis crónica, enfisema pulmonar o dispnea, reacciones alérgicas (por ejemplo rinitis, respuestas inducidas por hiedra venenosa, urticaria, escleroderma, artritis) otras enfermedades auto inmunes, enfermedad inflamatoria del intestino, enfermedad de Addison, enfermedad de Crohn, soriasis, reumatismo, hipertensión, desordenes de la función neurológica, glaucoma y diabetes (K.N. Klotz, Naunyn-Schmiedberg's Arch.farmacol. 362:382,2000; P.G. Baraldi es P:A: Borea, TiPs 21:456,2000).

Los compuestos de la presente invención puede ser preferiblemente utilizados para el tratamiento de enfermedad tal como asma, COPD y ARDS, glaucoma, tumor, enfermedad alérgica e inflamatoria, isquemia, hipoxia, arritmia y enfermedades renales.

De acuerdo con otro de sus aspectos, la presente invención se relaciona con el uso de los compuestos de la fórmula general (I) en el tratamiento de las patologías anteriores. La dosis diaria sugerida es de 1-100 mg de ingrediente activo dependiendo de la naturaleza de la severidad de la enfermedad y del sexo, peso, etc. del paciente.

Un objeto adicional de la invención es la preparación de los compuestos de la fórmula general (I) y los intermedios de las fórmulas generales (II) (III) y (IV).

Los intermedios de las fórmulas generales (II), (III) y (IV) que son utilizados en el proceso de preparación de acuerdo con la invención, son novedosos. Los sustituyentes de las fórmulas generales (II), (III) y

(IV) tienen los significados como se definieron anteriormente.

En el proceso de acuerdo con nuestra invención la bis-carboxamida de la fórmula general (II) es selectivamente hidrolisada y el compuesto resultante a la fórmula general (I) es, si se desea, transformado en sus sales, solvatos o, liberado de su sal como solvato y separada en sus isómeros geométricos u ópticos.

Los sustituyentes de los compuestos de la fórmula general (I) se pueden transformar uno en el otro mediante métodos conocidos.

La hidrólisis selectiva se desarrolla al utilizar solución alcohólica, preferiblemente solución de hidróxido alcalino metanolico, preferiblemente soluciones de potasio y/o sodio, pero otros agentes que ayudan la hidrólisis de las amidas también se puedan utilizar.

La hidrólisis selectiva se puede llevar a cabo en un amplio rango de temperaturas favorablemente entre 20 °C - 100 °C.

105

106

Los compuestos de la fórmula general (II)-en donde los significados R^1,R^2,R^3,R^4,R^5,R^6,R^8,X y n son como se definió anteriormente, se pueden obtener mediante varios métodos conocidos, entre ellos el demostrado en el esquema 1 (Figura 6), mediante la acilación del compuesto de fórmula (III), al utilizar un método de acilación conocido en la química orgánica. Para el agente de acilación preferiblemente cloruro de acilo, para el agente ácida trietilamina y/o piridina se pueden aplicar, pero también se puede utilizar otros agentes de unión ácida.

Los compuestos de la fórmula general (III)-en donde los significados R^1,R^2,R^3,R^4,R^5,R^6,R^8,X y n son como se definió anteriormente, se pueden preparar de los compuestos de la fórmula (IV)- al utilizar métodos conocidos per se (Nan Zhang, Bioorg. y Med. Chem. Lett., 10, 2825, 2000).

Los compuestos de la fórmula general (IV)-en donde los significados R^4,R^5 y R^6 son como se definió anteriormente - se pueden preparar de los compuestos de la fórmula (V), al utilizar métodos conocidos per se (D.L: Leysen, J. Heterocyclic Chem., 24, 1611, 1987).

106

107

Los compuestos de la fórmula general (V)-en donde los significados R^4,R^5 y R^6 son como se definió anteriormente - se pueden preparar de los compuestos de la fórmula (VI), al utilizar métodos conocidos per se (Pfizer (Inc) USP 4, 175, 193).

Los compuestos de la invención de las fórmulas generales (I), (II), (III) y (IV), u preparación y su actividad biológica son demostrados en los siguientes ejemplos, sin limitar el alcance de las reivindicaciones a los ejemplos.

La figura 1 muestra la fórmula general (I), la figura 2 muestra la fórmula general (IA), la figura 3 muestra la fórmula general (II), la figura 4 muestra la fórmula general (III) y la figura 5 muestra la fórmula general (IV). La figura 6 muestra el esquema 1 la ruta de reacción para la preparación de los compuestos de la fórmula general (I).

Ejemplos 1

107 138

3-Metil-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida:

En la fórmula general (I) R^1 y R^2 representa átomos de hidrogeno, R^3 representan grupo fenilo, R^4 y R^5 forman juntos un grupo 1,3-butadienilo, R^6 representa grupo ciano, R^7 representa un grupo 3-metilfenilo, el significado de X es el grupo -NH-, n es 1.

a) 2-Amino-3-ciano-4-cloroquinolina:

La mezcla 10 g de 2-amino-3-ciano-4-hidroxiquinilina y 15 ml de cloruro de fosforilo se calientan bajo agitación a 110 °C. la mezcla de reacción se enfria, se vierte sobre 100 ml de hielo-agua y se neutraliza con 60 ml de una solución de hidróxido de sodio al 10%. El precipitado amarillo resultante se filtra, se lava con 50 ml de agua. Después de secado 7,5 g del compuesto del título se obtienen, pf.: 210 °C.

NMR, δ_H(400 MHz, DMSO-d_6): 57,21 ppm,(s, 2H, NH_2), 7,35-7,40 ppm, (dd, 1H, 6-H), 7,53-7,57 ppm, (d, 1H, 5-

H), 7,70-7,75 ppm, (dd, 1H, 7-H), 7,93-7,98 ppm, (d, 1H, 8-H)

b) 2-Amino-3-ciano-4-benzilaminoquinolina

5 g de 2-amino-3-ciano-4-cloroquinolina y 11 ml de benzilamina son calentados bajo agitación a 130 °C. la mezcla de reacción se vierte sobre 50 ml de agua, el precipitado resultante se filtra, se lava con 50 ml de agua, el precipita amarillo pálido se recristaliza de metilformamida para obtener 5,2 g del compuesto del título.

NMR, δ_H(400 MHz, DMSO-d_6):5,02-5,03 ppm, (d, 2H, N-CH_2), 6,22 ppm, (s, 2H, NH_2), 7,14-7,16 ppm, (dd, 1H, 6-H), 7,24-7,26 ppm, (dd, 1H, 5-H), 7,30 ppm, (s, 5H, Ph), 7,50-7,52 ppm,(dd, 1H, 7-H), 8,16-8,19 ppm, (d, 1H, 8-H), 8,30-8,33 ppm, (t, 1H, NH)

Utilizando 2-aminometilpiridina o 3-aminometilpiridina o 4-aminometilpiridina en lugar de benzilamina, los compuestos apropiados de la fórmula general III se pueden obtener.

c) 3-metil-N-(3-metilbenzoil)-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida:

A la solución 5 g de 2-amino-3-ciano-4-benzilaminoquinolina en 30 ml de piridina se gotean 6 ml de 3-metilbenzoil cloruro, bajo agitación a 0 °C. La mezcla de reacción se agita a 80 °C duran te 8h, luego se vierten sobre 150 ml de hielo-agua, el precipitado resultante se filtra, se lava dos veces con 40 ml de agua, el material cristalino blanco resultante se recristaliza de 200 ml de etanol para dar 9,2 g del compuesto del título, pf.: 234 °C.

Al utilizar cloruro de piridina-3-carbonilo como agente acilante, el compuesto apropiado de la fórmula general II se puede obtener.

d) 3-metil-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida

A la solución 5 g de 3-metil-N-(3-metilbenzoil)-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida en 80 ml de acetonitrilo 20 ml de solución de hidróxido de

potasio metanólico 1N se agregan. La mezcla de reacción se refluye durante 3 minutos, luego 3 ml de ácido acético glacial se agregan a esta, luego se neutralizan con 50 ml de una solución de carbonato ácido de hidrogeno 1M y los cristales resultantes se filtran. El material cristalino blanco se recristaliza de 130 ml de acetonitrilo para dar 3,1 g del compuesto del título de fórmula general (I). Pf.: 230 °C.

Ejemplo 2

4-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo fenilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 representa grupo ciano, R^7 representa un grupo 4-metoxifenilo, el significado de X es el grupo -NH-, n es 1.

2-amino-3-ciano-4-benzilaminoquinilina, preparado como se describió en el ejemplo 1, se transforma con

cloruro de 4-metoxibenzoilo análogamente como se describió en el ejemplo 1, en 4-metoxi-N-(4-metoxibenzoil)-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida, el cual después de hidrólisis selectiva, mediante el método descrito en el ejemplo 1, da como resultado el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 188 °C.

La sal de sodio del compuesto del título se prepara mediante el siguiente método:

4-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida se disuelve en metanol y una cantidad equivalente de hidróxido de sodio en metanol se agrega a esta. El material cristalino blanco precipitado se filtra. Pf. 255 °C.

Sal de etanosulfonato del compuesto del título se prepara del siguiente método:

4-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il) benzamida se disuelve en metanol y cantidad equivalente de ácido etanosulfonico se agrega a esta.

El material cristalino blanco resultado se filtra. Pf.: 223 °C.

Ejemplo 3

3-metoxi-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo fenilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 3-metoxifenilo, el significado de X es el grupo -NH-, n es 1.

2-amino-3-ciano-4-benzilaminoquinolina, preparado como se describió en el ejemplo 1, se transforma con cloruro de 3-metoxibenzoilo análogamente como se describió en el ejemplo 1, en 3-metoxi-N-(3-metoxibenzoil)-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida, el cual después de hidrólisis selectiva, mediante el método descrito en el ejemplo 1, da como resultado el compuesto del título de fórmula general

~~113~~ 114

(I). El punto de fusión del compuesto del título: 186 °C.

Ejemplo 4

3,4-metilenedioxy-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo fenilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 3,4-metilenedioxifenilo, el significado de X es el grupo -NH-, n es 1.

2-amino-3-ciano-4-benzilaminoquinolina, preparado como se describió en el ejemplo 1, se transforma con cloruro de 4-metoxibenzoilo análogamente como se describió en el ejemplo 1, en 3-metilenedioxi-N-(3,4-metilenedioxibenzoilo)-N-(4-benzilamino-3-cianoquinolin-2-il)benzamida, el cual después de hidrólisis selectiva, mediante el método descrito en el ejemplo 1; da como resultado el compuesto del

título de fórmula general (I). El punto de fusión del compuesto del título: 231 °C.

Ejemplo 5

N-(4-benzilamino-3-cianoquinolin-2-il)tiofeno-2-carboxamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo fenilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 2-tienilo, el significado de X es el grupo -NH-, n es 1.

2-amino-3-ciano-4-benzilaminoquinolina, preparado como se describió en el ejemplo 1, se transforma con cloruro de tiofeno-2-carbonilo, análogamente como se describió en el ejemplo 1, en N-(2-tiofenocarbonil)-N-(4-benzilamino-3-cianoquinolin-2-il)tiofeno-2-carboxamida, el cual después de hidrólisis selectiva, mediante el método descrito en el ejemplo 1; da como resultado el compuesto del título de fórmula general

(I). El punto de fusión del compuesto del título: 197 °C.

Ejemplo 6

N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)tiofeno-3-carboxamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo 2-tienilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 3-tienilo, el significado de X es el grupo -NH-, n es 1.

a) 2-amino-3-ciano-4-(2-tienilmetilamino)quinolina

5 g de 2-amino-3-ciano-4-cloroquinolina preparada como se describió en el ejemplo 1 se agitan con 11 ml de 2-tienilmetilamino a 130 °C durante 3h. La mezcla de reacción se vierte sobre 50 ml de agua el precipitado resultante se filtra, se lava con 50 ml de agua. El material amarillo pálido se recristaliza de

116

117

25 ml de etanol para obtener 5,2 g del compuesto del título se obtienen, pf.: 208 °C.

La 2-amino-3-ciano-4-(2-tienilmetilamino)quinolina preparada como se describió anteriormente se transforma con cloruro de tiofeno -3-carbonilo, análogamente como se describió en el ejemplo 1, en N-(3-tiofenocarbonil)-N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)tiofeno-3-carboxamida, el cual después de hidrólisis selectiva, mediante el método descrito en el ejemplo 1; da como resultado el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 223 °C.

Ejemplo 7

4-metoxi-N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)benzamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo 2-tienilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 4-

metoxifenil, el significado de X es el grupo -NH-, n es 1.

La 2-amino-3-ciano-4-(2-tienilmetilamino)quinolina preparada como se describió en el ejemplo 6, se transforma con cloruro de 4-metoxibenzoilo en 4-metoxi-N-metoxibenzoil)-N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)benzamida, mediante el método descrito en el ejemplo 1, el cual después de hidrólisis selelctiva da el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 173 °C.

Ejemplo 8

3,4-metilenedioxi-N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)benzamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo 2-tienilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 3,4-metilenedioxifenilo, el significado de X es el grupo -NH, n es 1.

2-amino-3-ciano-4-(2-tienilmetilamino)quinolina preparada como se describió en el ejemplo 6, transforma con cloruro de 3,4-metilenedioxibenzoilo en 3,4-metilenedioxi-N-(3,4-metetilenedioxibenzoilo)-N-(4-[2-tienilmetilamino]-3-cianoquinolin-2-il)benzamida, mediante el método descrito en el ejemplo 1, el cual después de hidrólisis selectiva da el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 241 °C.

Ejemplo 9

N-(4-[2-furilmetilamino]-3-cianoquinolin-2-il)furan-2-carboxamida

En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo 2-furilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 2-furilo, el significado de X es el grupo -NH-, n es 1.

a) 2-amino-3-ciano-4-(2-furilmetilamino)quinolina

5 g de 2-amino-3-ciano-4-cloroquinolina preparada como se describió en el ejemplo 1 se agitan con 1 ml de 2-furilmetilamina (furfurilamina) a 130 °C durante 3h. La mezcla de reacción se vierte sobre 50 ml de agua, el precipitado resultante se filtra, se lava con 50 ml de agua. El material amarillo pálido se recristaliza de 20 ml de etanol para obtener 4,8 g del compuesto del título, pf.: 208 °C.

La 2-amino-3-ciano-4-(2-furimetilamino)quinolina preparada como se describió anteriormente se transforma con cloruro de furan-2-carbonilo, mediante el método descrito en el ejemplo 1, N-(2-furancarbonil)-N-(4-[2-furilmetilamino]-3-cianoquinolin-2-il)furan-2-carboxamida, el cual después de hidrólisis selectiva, da como resultado el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 196 °C.

Ejemplo 10

N-(4-[2-furilmetilamino]-3-cianoquinolin-2-il)tiofeno-3-carboxamida

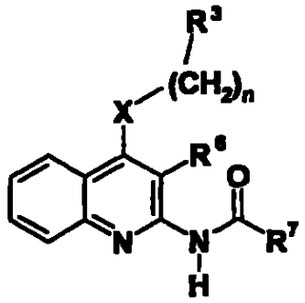
En la fórmula general (I) el significado R^1 y R^2 es átomos de hidrogeno, R^3 es grupo 2-furilo, R^4 y R^5 significan juntos un grupo 1,3-butadienilo, R^6 significa grupo ciano, R^7 significa un grupo 3-tienilo, el significado de X es el grupo -NH-, n es 1.

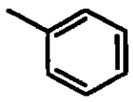
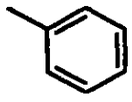
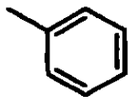
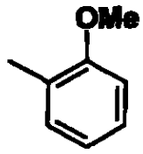
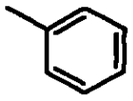
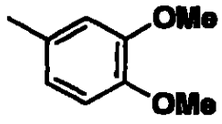
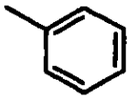
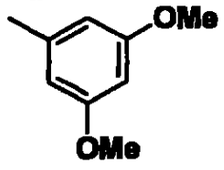
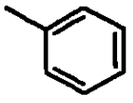
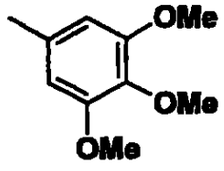
1. La 2-amino-3-ciano-4-(2-furimetilamino)quinolina preparada análogamente como se describió en el ejemplo 6, se transforma con cloruro de tiofeno-3-carbonilo, mediante el método descrito en el ejemplo 1. En N-(3-tiofenocarbonil)-N-(4-[2-furilmetilamino]-3-cianoquinolin-2-il)tiofeno-3-carboxamida, el cual después de hidrólisis selectiva, desarrollada análogamente como se describió en el ejemplo 1 da el compuesto del título de fórmula general (I). El punto de fusión del compuesto del título: 118 °C.

La estructura y las características físicas de los compuestos adicionales de la fórmula general (I) preparado por el método descrito en el ejemplo 1, son mostrados en las tablas I y II.

124
122

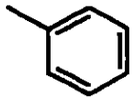
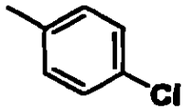
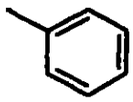
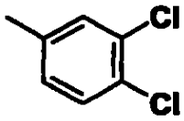
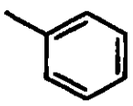
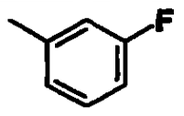
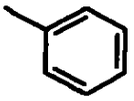
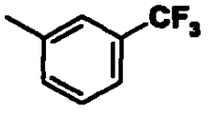
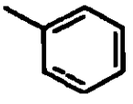
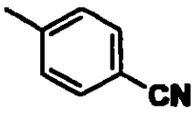
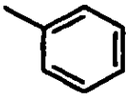
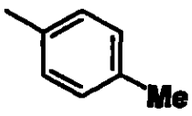
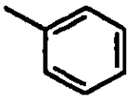
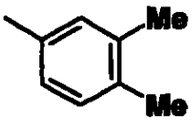
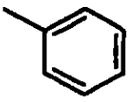
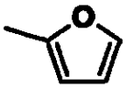
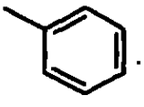
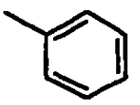
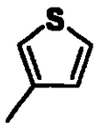
TABLA I



No.:	X	R^3	R^6	R^7	n	Mp [°C]
11.	NH		CN		1	237
12.	NH		CN		1	128
13.	NH		CN		1	116
14.	NH		CN		1	100,5
15.	NH		CN		1	223

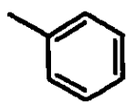
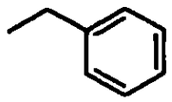
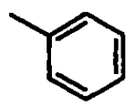
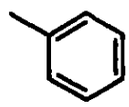
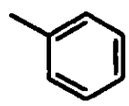
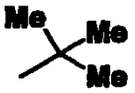
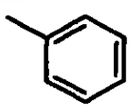
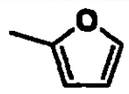
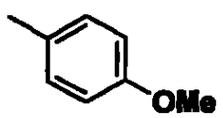
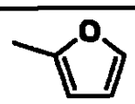
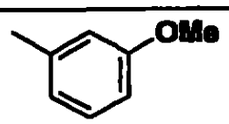
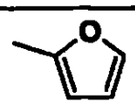
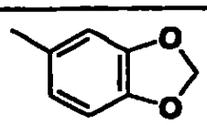
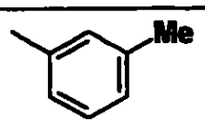
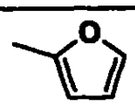
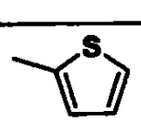
122

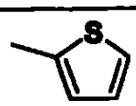
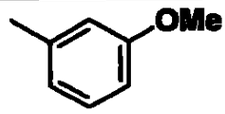
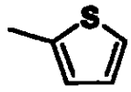
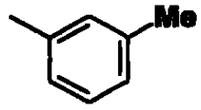
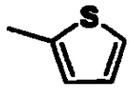
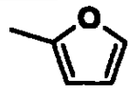
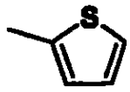
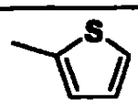
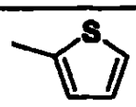
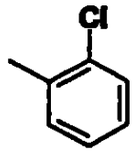
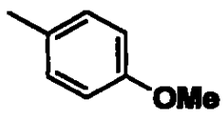
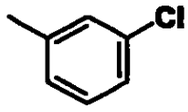
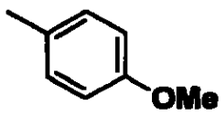
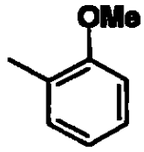
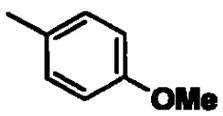
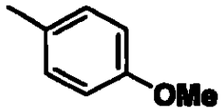
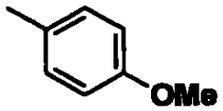
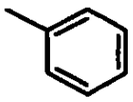
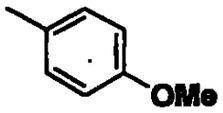
123

16.	NH		CN		1	193,5
17.	NH		CN		1	193
18.	NH		CN		1	208
19.	NH		CN		1	215
20.	NH		CN		1	250
21.	NH		CN		1	205
22.	NH		CN		1	238
23.	NH		CN		1	212
24.	NH		CN		1	215
25.	NH		CN		1	234

123

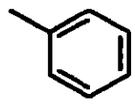
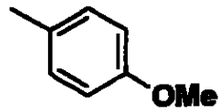
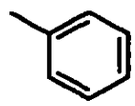
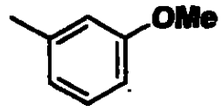
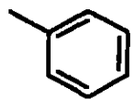
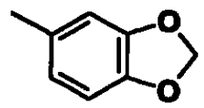
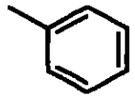
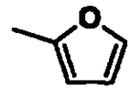
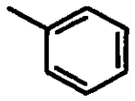
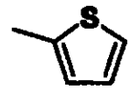
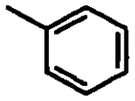
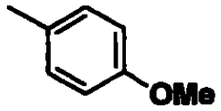
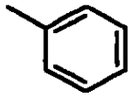
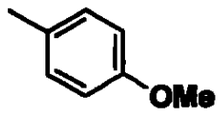
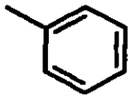
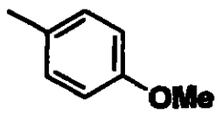
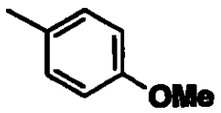
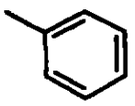
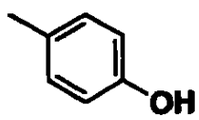
124

26.	NH		CN		1	160,5
27.	NH		CN	—Me	1	184
28.	NH		CN		1	141,5
29.	NH		CN		1	194
30.	NH		CN		1	203
31.	NH		CN		1	152
32.	NH		CN		1	190
33.	NH		CN		1	202
34.	NH		CN		1	207
35.	NH		CN		1	159
36.	NH		CN		1	200

37.	NH		CN		1	206
38.	NH		CN		1	221
39.	NH		CN		1	198
40	NH		CN		1	158
41.	NH		CN		1	178
42.	NH		CN		1	198,5
43.	NH		CN		1	197,5
44.	NH		CN		1	191
45.	NH		CN		1	168,5
46.	N-Me		CN		1	155

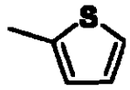
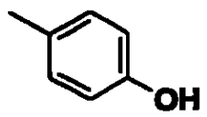
125-

126

47.	NH		H		1	172
48.	NH		H		1	250
49.	NH		H		1	264
50.	NH		H		1	265
51.	NH		H		1	163
52.	O		CN		1	157
53.	S		CN		1	196
54.	S=O		CN		1	205
55.	NH	H	CN		0	266
56.	NH		CN		1	154

-126-

129

57	NH		CN		1	145

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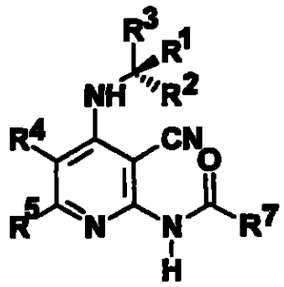

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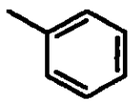
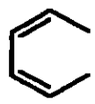
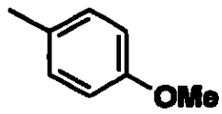
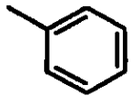
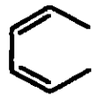
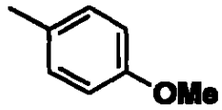
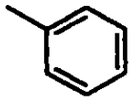
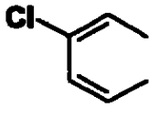
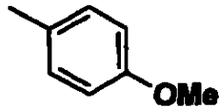
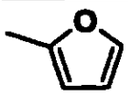
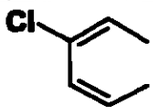
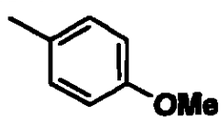
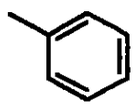
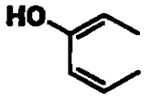
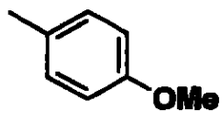
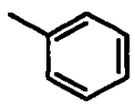
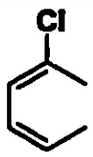
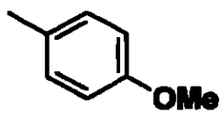
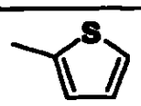
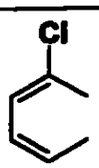
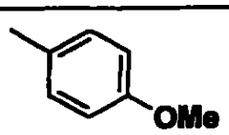
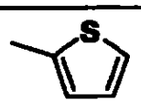
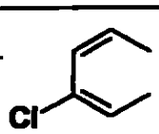
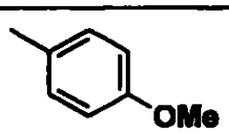
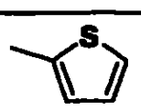
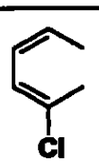
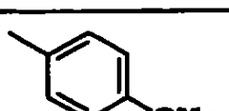
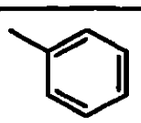
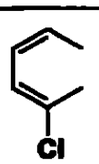
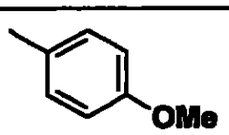
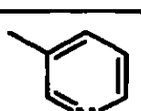
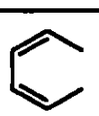
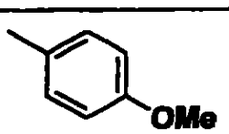
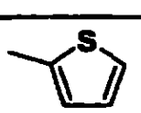
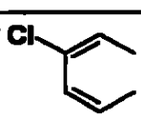
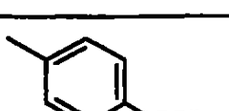
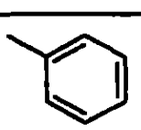
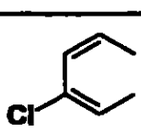
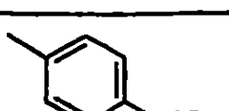
58.	Me	H					165
59.	H	Me					145
60.	H	H					119
61.	H	H					119

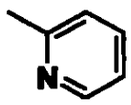
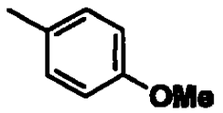
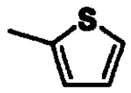
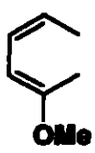
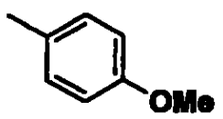
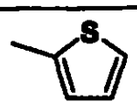
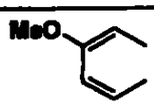
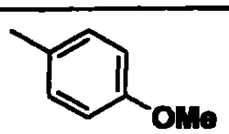
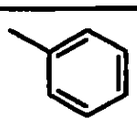
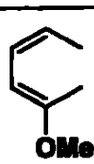
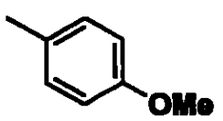
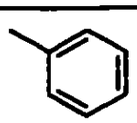
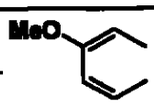
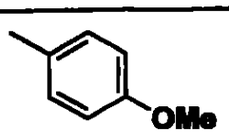
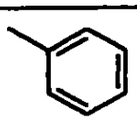
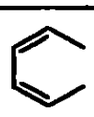
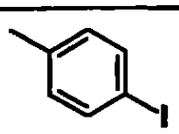
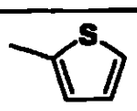
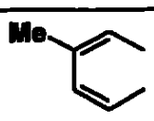
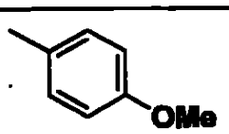
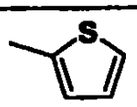
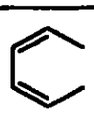
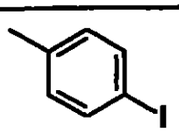
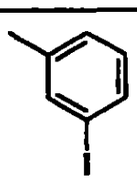
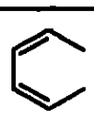
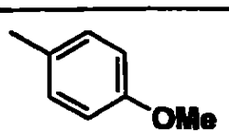
127

128

62.	H	H				243
63.	H	H				176
64.	H	H				171
65.	H	H				199
66.	H	H				203
67.	H	H				180
68.	H	H				117
70.	H	H				153
71.	H	H				215

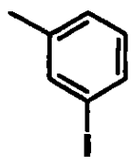
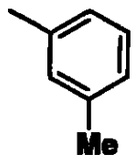
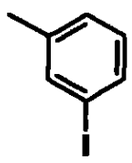
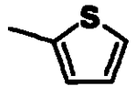
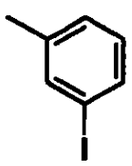
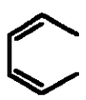
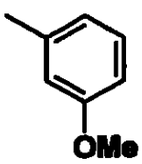
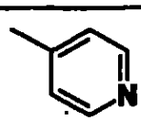
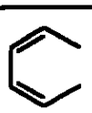
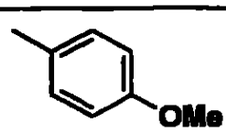
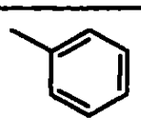
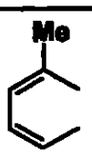
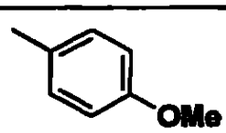
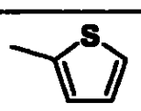
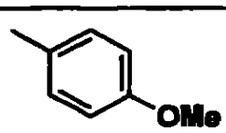
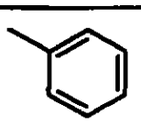
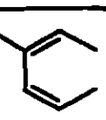
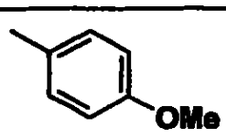
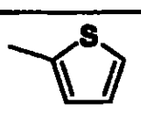
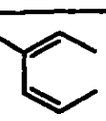
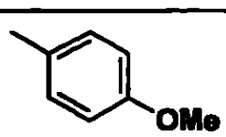
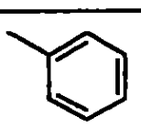
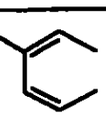
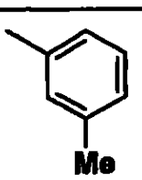
128

129

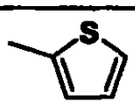
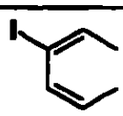
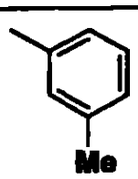
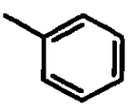
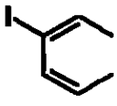
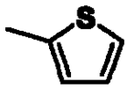
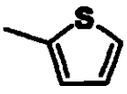
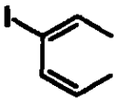
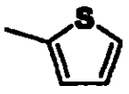
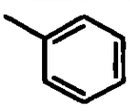
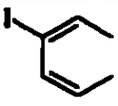
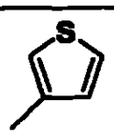
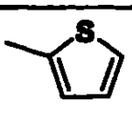
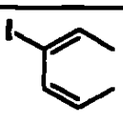
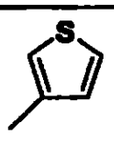
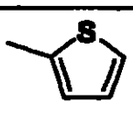
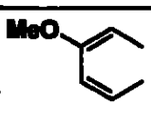
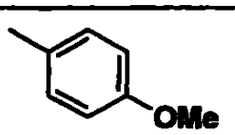
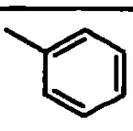
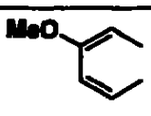
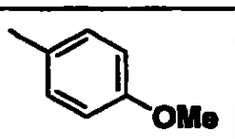
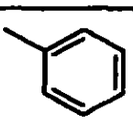
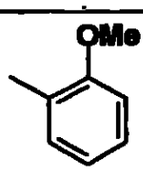
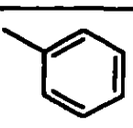
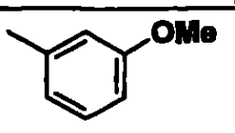
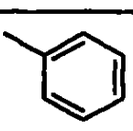
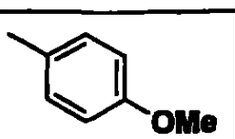
72.	H	H				237
73.	H	H				275
74.	H	H				245
75.	H	H				247
76.	H	H				222
77.	H	H				218
78.	H	H				214
79.	H	H				252
80.	H	H				178

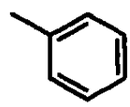
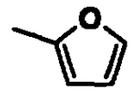
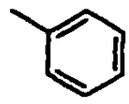
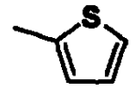
129

130

81.	H	H				173
82.	H	H				212
83.	H	H				184
84.	H	H				150
85.	H	H				195
86.	H	H				171
87.	H	H				217
88.	H	H				149
89.	H	H				135

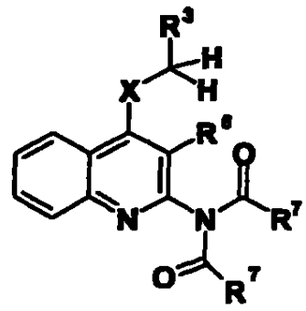
130
131

90.	H	H				127
91.	H	H				257
92.	H	H				260
93.	H	H				153
94.	H	H				145
95.	H	H				214
96.	H	H				183
97.	H	H		H	H		167
98.	H	H		H	H		162
99.	H	H		H	H		183

100	H	H		H	H		216
101	H	H		H	H		206

La estructura y las características físicas de los intermedios de la fórmula general (II) preparados por el método descrito en el Ejemplo 1. Se muestran en la Tabla III.

Tabla III



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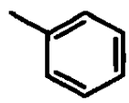
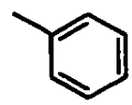
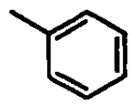
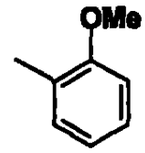
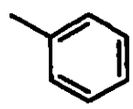
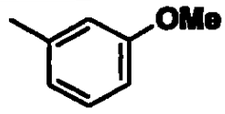
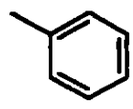
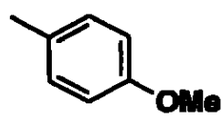
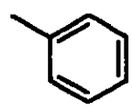
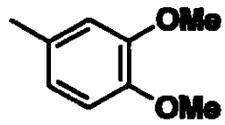
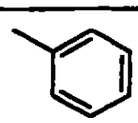
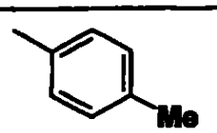
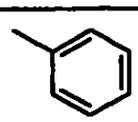
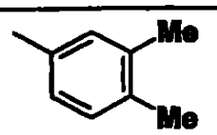
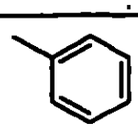
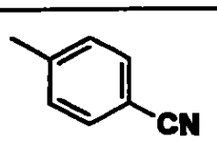
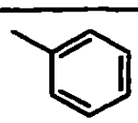
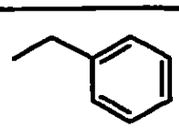
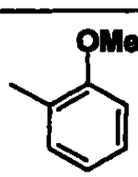
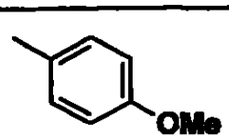
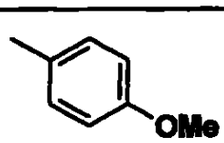
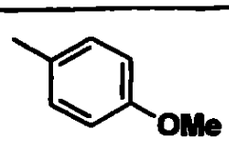
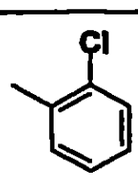
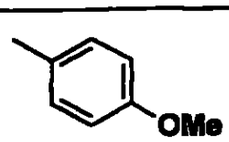
102	NH		CN		213
103.	NH		CN		208

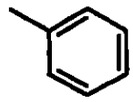
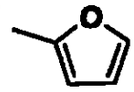
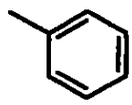
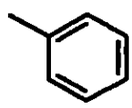
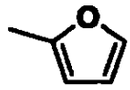
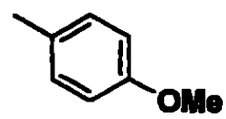
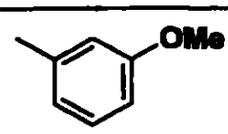
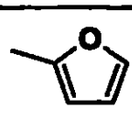
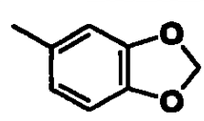
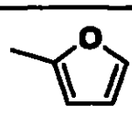
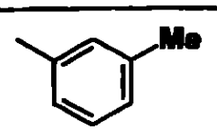
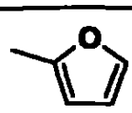
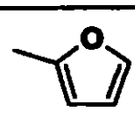
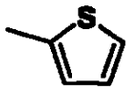
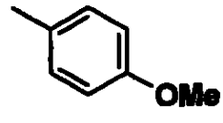
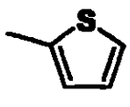
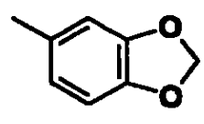
132

133

104	NH		CN		178s
105	NH		CN		158
106	NH		CN		210
107	NH		CN		223
108	NH		CN		224
109	NH		CN		212
110	NH		CN		198
111	NH		CN		208
112	NH		CN		168
113	NH		CN		168

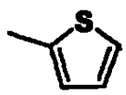
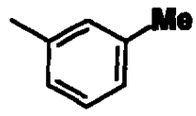
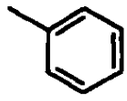
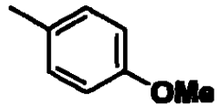
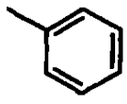
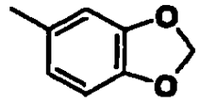
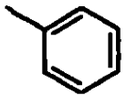
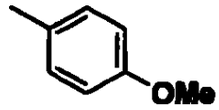
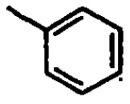
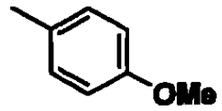
133

134

114	NH		CN		225
115	NH		CN	Me	152
116	NH		CN	Et	192
117	NH		CN		177
118	NH		CN		169
119	NH		CN		151
120	NH		CN		218
121	NH		CN		194
122	NH		CN		188
123	NH		CN		179

134

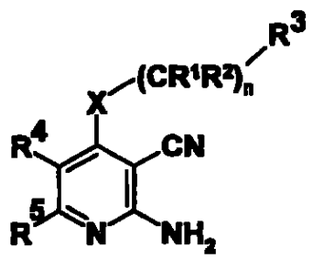
135

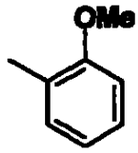
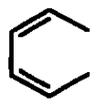
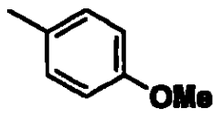
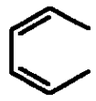
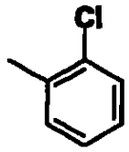
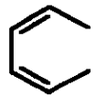
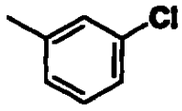
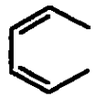
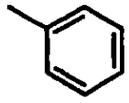
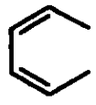
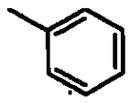
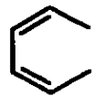
124	NH		CN		239
125	NH		H		162
126	NH		H		262
127	S		CN		170
128			CN		228

La estructura y las características físicas de los intermedios de la fórmula general (III) y (IIIa) preparados mediante el método descrito en el ejemplo 1. Se muestran en la tabla IV.

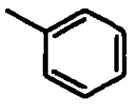
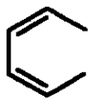
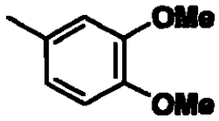
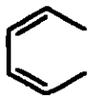
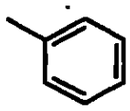
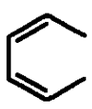
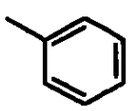
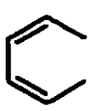
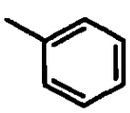
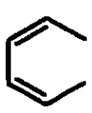
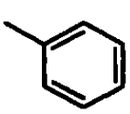
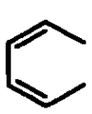
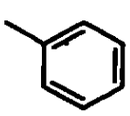
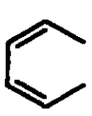
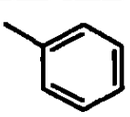
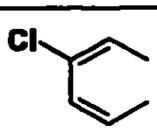
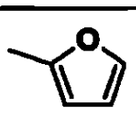
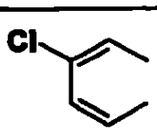
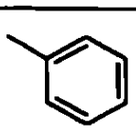
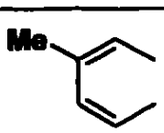
~~135~~ 136

Tabla IV



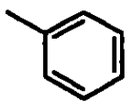
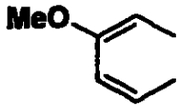
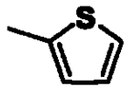
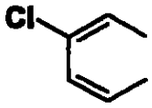
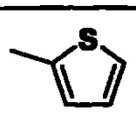
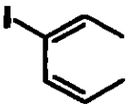
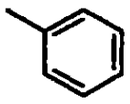
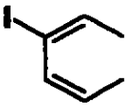
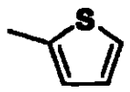
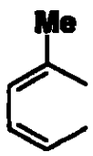
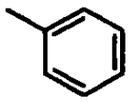
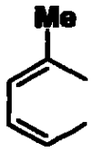
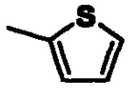
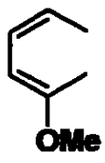
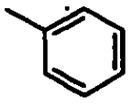
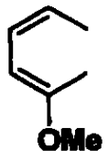
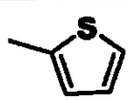
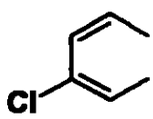
No.:	R^1	R^2	R^3	R^4	R^5	X	n	Mp [°C]
129	H	H				NH	1	192
130	H	H				NH	1	202
131	H	H				NH	1	250
132	H	H				NH	1	167
133	H					NH	1	183
134	H					NH	1	182

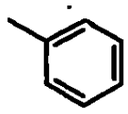
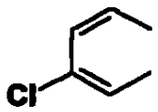
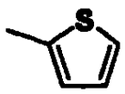
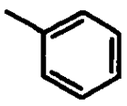
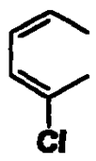
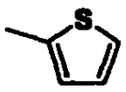
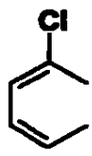
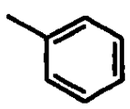
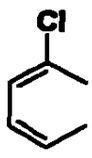
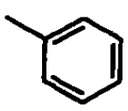
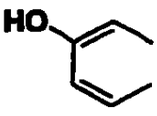
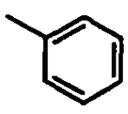
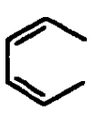
~~136~~ 137

135	H	H			NH	2	172
136	H	H			NH	2	143
137	H				NH	2	129
138	H				NH	2	136
139	H	H			N-Me	1	212
140	H	H			S	1	168
141	H	H			O	1	213
142	H	H			NH	1	234
143	H	H			NH	1	221
144	H	H			NH	1	198

137

138

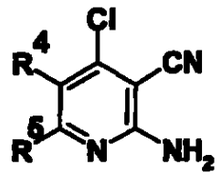
145	H	H			NH	1	201
146	H	H			NH	1	213
147	H	H			NH	1	198
147	H	H			NH	1	201
148	H	H			NH	1	167
149	H	H			NH	1	156
150	H	H			NH	1	187
151	H	H			NH	1	178
152	H	H			NH	1	207

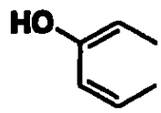
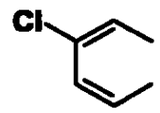
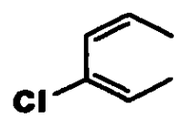
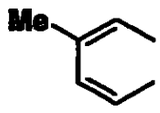
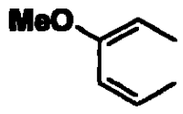
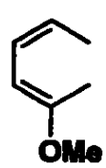
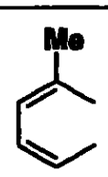
153	H	H			NH	1	217
154	H	H			NH	1	204
155	H	H			NH	1	216
156	H	H			NH	1	205
158	H	H			NH	1	213
159	H	H			NH	1	200
160					NH	0	214

Estructura y características físicas de los intermedios de la fórmula general (V) preparados mediante el método descrito en el ejemplo 1, se muestran en la tabla V.

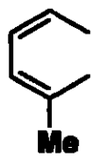
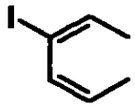
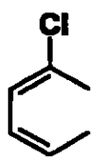
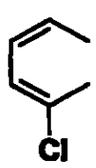
139
140

TABLA V



No:	R^4 R^5	Mp [°C]
161.		360
162.		250
163.		278
164		283
165.		360
166.		234
167		246

140-
141

168		267
169		293
170		289
171		307

Ejemplo 172.

Las tabletas de la siguiente composición son hechas mediante métodos conocidos utilizados en la industria farmacéutica

Ingrediente Activo	25 mg
Lactosa	50 mg
Avicel	21 mg
Crospovidona	3 mg
Estearato de magnesio	1 mg

Biología

Métodos

Unión de receptor de A_3 adenosina humano

Preparación de suspensión de membrana: recolectar células CHO que expresan receptores hA3 al lavar tres veces con hielo PBS frío, centrifuga a 1000 x g 10 min, homogenizar durante 15 sec en amortiguador (50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, pH 8.09), centrifuga a 43.000 x g durante 10 min (Sigma 3K30), suspender la

142 143

preparación de membrana en amortiguador mencionado anteriormente, almacenar las alícuotas a -80 C.

Protocolo de unión: incubar la preparación de membrana CHO-hA_3 (contenido de proteína 2 µg) en amortiguador de incubación (50mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, 3 U/mL adenosina deaminasa, pH 8.0),en la presencia de 0,5 nM [^{125}]AB-MECA (p-amino-benzilo-metilcarboxamido-adenosina) (100.000 cpm) y 100 µM R-PIA (N^6-[L-2-fenilisopropil]adenosina) para definir una unión no especifica o un compuesto de ensayo en un volumen total de 50 µL durante 1 hr a temperatura ambiente. Filtrar sobre filtros de fibra de vidrio Whatman GF/B (preempapado en 0,5% de polietilenimina durante 3 horas), lavar 4x con 1 mL de hielo- 50 mM de Tris frío, 10 mM $MgCl_2$, 1 mM EDTA (pH 8.0) sobre un cosechador de celda Brandel de 96 posos. Detección de actividad: en contador gama (1470 Wizard, Wallac). Inhibición [%]= 100-((actividad en la presencia del compuesto de ensayo - actividad no especifica)/(actividad total-actividad no especifica))*100

143
144

Unión de receptor A_1 de adenosina humana

Preparación de suspensión de membrana: recolectar células CHO que expresan receptores hA_1 al lavar tres veces con hielo PBS frio, centrifuga a 1000 x g 10 min, homogenizar durante 15 sec en amortiguador (50 mM Tris, pH 7,4), centrifuga a 43.000 x g durante 10 min (Sigma 3K30), suspender la preparación de membrana en amortiguador mencionado anteriormente, almacenar las alícuotas a -80 C.

Protocolo de unión: incubar la preparación de membrana CHO-hA_1 (contenido de proteína 50 µg) en amortiguador de incubación (50 mM Tris, 3 U/mL de adenosina deaminasa, pH 7.4), 10 nM [^{3}H]CCPA (2-cloro-N^6-ciclofenil-adenosina)

(80.000 dpm) y 10 µM R-PIA (N^6-[L-2-fenilisopropil] adenosina) para definir el compuesto de unión de ensayo no especifica en un volumen total de 100 µL durante 3 hr a temperatura ambiente de cuarto. Filtrar sobre filtros de fibra de vidrio Whatman GF/B (preempapados en 0,5% de polietilenimina durante 3 horas), lavar 4x con 1 mL de hielo- 50 mM de

Tris frío, (pH 7,4) sobre un cosechador de celda Brandel de 96 posos. Detección de actividad: en

un plato de 96 posos en la presencia de un cóctel HiSafe-3 en un contador beta (1450 Microbeta, Wallac). Inhibición [%]= 100-((actividad en la presencia del compuesto de ensayo - actividad no especifica)/(actividad total-actividad no especifica))*100

Unión de receptor A_{2a} de adenosina humana

Protocolo de unión: incubar 7 µg de membranas (receptores de adenosina A_{2a} humano tranfectada en HEK-293, fuente: Receptor Biology, Inc), amortiguador (50 mM Tris-HCI, 10 mM $MgCl_2$, 1 mM EDTA, 2 U/mL de adenosina deaminasa, pH 7,4), 20 nM [^{3}H]CGS-21680 (2-[p-(2-carboniletil)feniletilamino]-5'-N-etilcarboxamido-adenosina) (200.000 dpm) y 50 µM NECA (5'-N-etilcarboxamido-adenosina)para definir la unión no especifica o compuesto de ensayo en un volumen total de 100 µL durante 90 min a temperatura ambiente de cuarto. Filtrar sobre filtros de fibra de vidrio Whatman GF/B (preempapados en 0,5% de

polietilenimina), lavar 4x con 1 mL de hielo- 50 mM de Tris frío, 10 mM $MgCl_2$, 1 mM EDTA, 0,9% NaCl, pH 7,4 sobre un cosechador de celda Brandel de 96 posos. Detección de actividad: en un plato de 96 posos en la presencia de un cóctel HiSafe-3 en un contador beta (1450 Microbeta, Wallac). Inhibición [%]= 100-((actividad en la presencia del compuesto de ensayo - actividad no especifica)/(actividad total-actividad no especifica))*100

Unión de receptor A_{2b} de adenosina humana

Protocolo de unión: incubar 20,8 µg de membranas (receptores de adenosina A_{2b} humano transfectadas en celulas HEK-293, fuente: Receptor Biology, Inc), amortiguador (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EDTA, 0,1 nM benzamidina, 2 U/mL de adenosina deaminasa, pH 6,5), 32,4 nM [^{3}H]DPCPX (8-ciclopentil-1,3-dipropilxantina) (800.000 dpm) y 100 µM NECA (5'-N-etilcarboxamido-adenosina)para definir la unión no especifica o compuesto de ensayo en un volumen total de 100 µL durante 30 min a temperatura ambiente. Filtrar sobre filtros de fibra de vidrio Whatman GF/C (preempapados en 0,5% de polietilenimina), lavar 4x

146 147

con 1 mL de hielo- 50 mM de Tris-HCl (pH 6,5) sobre un cosechador de celda Brandel de 96 posos. Detección de actividad: en un plato de 96 posos en la presencia de un cóctel HiSafe-3 en un contador beta (1450 Microbeta, Wallac). Inhibición [%]= 100-((actividad en la presencia del compuesto de ensayo - actividad no especifica)/(actividad total-actividad no especifica))*100

Resultados

Consideramos los compuestos como biológicamente activos se ellos inhiben la unión del radioligandos sobre los receptores A_3 de adenosina humana con una actividad superior al 80% a 1 μM en nuestras condiciones experimentales.

La constante de disosaciación (K_d) de [^{125}I]AB-MECA sobre reparación de CHO-hA_3 se determina mediante estudios de saturación de isótopo con la ayuda de análisis Scatchard (G. Scatchard, Ann. N. Y. Acad. Sci. 51:660, 1949). El IC_{50} se convierte a una constante de afinidad (K_i) mediante la aplicación de

147

148

una adecuación Cheng-Prusoff (Y. J. Cheng y W.H: Prusoff, Biochem. Pharmacol. 22:3099, 1973).

Varios compuestos de la fórmula general (I),(II),(III) y (IV) muestran efectos biológicos notorios. Los compuestos de la formula general (IA), definido en la reivindicación 2, como el subgrupo de la formula general (I), definido en la reivindicación 1, ejercen las actividades más importantes. Excepto los compuestos 5, sus valore K_i no son más altos de 20 nM. Los compuestos dados como ejemplos son especialmente ventajosos. Sus valores K_i en los estudios de unión de receptor A_3 de adenosina humana están entre 0,19 y 0,69 nM. Los valores K_i de los compuestos más ventajosos son 0,14 y 0,15 nM.

Los compuestos poseen biodisponibilidades propias y ejercen al menos una selectividad de 10.000 veces con respecto a los subtipos de receptor A_1, A_{2a} y A_{2b} de adenosina humana.

Además, la duración de su acción en administración intravenosa y oral es suficientemente

148

149

larga, sus valores ED_{50} son bajos, sus perfiles toxicológicos y efectos colaterales son ventajosos.

Los datos anteriores hacen los compuestos de la fórmula general (I) probables para aplicaciones terapéuticas.

149 150

REIVINDICACIONES

1) compuestos de la fórmula general (I)- en donde

R^1 representa átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado;

R^2 representa átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado;

R^3 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante uno o más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de hidrógeno y un átomo de oxigeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático de 5 o 6 miembros, opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos alcoxxi C_{1-4} rectos o ramificados, o átomo de halógeno;

150 151

R^4 y R^5 representa átomos de hidrógeno o forma junto con el grupo 1, 3-butadienilo, opcionalmente sustituido mediante un grupo metilenedioxi o uno más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi o átomo de halógeno;

R^6 representa átomo de hidrógeno o grupo ciano, un grupo aminocarbonilo, un grupo alcoxicarbonilo C_{1-4} o un grupo a carboxi;

R^7 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo benzilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante un grupos metilenedixi o uno o más grupos alquilo C_{1-4} recto o ramificado, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de hidrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre que contienen anillos heteroaromáticos de 5 o 6 miembros, Opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos

~~151~~ 152

alcoxxi C_{1-4} rectos o ramificados, o átomo de halógeno;

X representa un grupo $-CH_2-$, grupo -NH-, grupo $-NR^8-$, o un átomo de azufre o un átomo de oxígeno o un grupo sulfo o un grupo sulfoxi- en donde R^8 representa un grupo alquilo C_{1-4} recto o ramificado o un grupo cicloalquilo $C_{3-6}-$;

n representa cero, 1 o 2- y sus sales, solvatos e isómeros óptimamente activos y sus sales , solvatos.

2) Compuestos de la fórmula general (IA) de acuerdo con la reivindicación 1- en donde

R^1 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado;

R^2 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado;

R^3 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo

tienilo, grupo furilo, opcionalmente sustituido mediante un o más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno, o representan uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre que contienen anillo heteraromático de 5 o 6 miembros opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno;

R^9, R^{10}, R^{11} y R^{12} representan independientemente uno de otro átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado, o grupo alcoxi C_{1-4} recto o ramificado, o grupo hidroxi o átomo de halógeno, o

R^9, y R^{12} representan átomo de hidrógeno y R^{10} y R^{11} forman juntos un grupo metilenedioxi;

R^6 representan átomo de hidrógeno o grupo ciano, grupo aminocarbonilo, grupo alcoxicarbonilo C_{1-4}, o grupo carboxi;

153

154

R^7 representan átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado, un grupo fenilo, grupo benzilo, grupo tienilo, grupo furilo, opcionalmente sustituido mediante un grupo metilenedioxy, o uno o más grupos alquilo C_{1-4} recto o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o representa uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre que contienen anillo heteroaromático de 5 6 miembros que contiene - opcionalmente sustituido con uno o más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno;

X representa un grupo $-CH_2-$, grupo -NH-, grupo $-NR^8-$, o un átomo de azufre o un átomo de oxígeno o un grupo sulfo o un grupo sulfoxi- en donde R^8 representa un grupo alquilo C_{1-4} recto o ramificado o un grupo cicloalquilo C_{3-6}-;

n representa cero, 1 o 2- y su sales, solvatos e isómeros óptimamente activos y sus sales y solvatos.

154
155

3) Compuestos de la fórmula (IA) de acuerdo a la reivindicación 2, en donde

R^1 representa átomo de hidrógeno, o un grupo metilo;

R^2 representa átomo de hidrógeno, o un grupo metilo;

R^3 representa grupo fenilo- o tienilo- o furilo;

R^9, R^{10}, R^{11}, y R^{12} representa independientemente uno del otro átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado, o grupo alcoxi C_{1-4} recto o ramificado, o grupo hidroxi o átomo de halógeno, o

R^9, y R^{12} representan átomo de hidrógeno y R^{10} y R^{11} forman juntos un grupo metilenedioxi;

R^6 representan átomo de hidrógeno, o grupo ciano;

R^7 representan 4-metoxifenilo-, 3-metifenilo-, , 3-tienilo-, o el grupo 3-furilo;

X representa un grupo -NH-, o átomo de oxígeno y

155

156

n representa 1-

y sus sales, sulfatos e isómeros óptimamente activos y sus sales y solvatos.

4) Compuestos de acuerdo a la reivindicación 1-3 como sigue:

3-metil-N-(4-benzilamino-3-ciano-quinolin-2-il) benzamida;

4-metoxi-N-(4-benzilamino-3-ciano-quinolin-2-il) benzamida;

3-metoxi-N-(4-benzilamino-3-ciano-quinolin-2-il) benzamida;

3, 4-metilenedioxi-N-(4-benzilamino-3-ciano-quinolin-2-il) benzamida;

N-(4-benzilamino-3-ciano-quinolin-2-il) tiofeno-2-carboxamida;

N-(4[2-tienilmetilamino] -3-ciano-quinolin-2-il) tiofeno-3-carboxamida;

4-metoxi-N-(4-[2- tienilmetilamino] -3-ciano-quinolin-2-il) benzamida;

156

157

3, 4-metilenedioxi-N-(4-[2- tienilmetilamino] -3-ciano-quinolin-2-il) benzamida;

N-(4[2-furilmetilamino]-3-ciano-quinolin-2-il) furan-2-carboxamida;

N-(4[2-furilmetilamino]-3-ciano-quinolin-2-il) tiofeno-3-carboxamida,

Y sus sales, solvatos, isómeros óptimamente activos y sus sales y solvatos.

5) Proceso para la preparación de un compuesto de fórmula general (I), sus sales, solvatos, isómeros óptimamente activos y sus sales y solvatos - en donde la fórmula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tiene los mismos significados como se definieron en la reivindicación 1, caracterizados por hidrólisis selectiva o una amida bis ácida de la fórmula general (II) -en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - y si se desea transformar los sustituyentes de los compuestos de

157

158

la fórmula general (I) así obtenida uno en el otro mediante los métodos conocidos per se y/o transformar el compuesto de fórmula general (I) así obtenido en sus sales, o solvatos, o liberar esta de sus sales o solvatos y/o depararla en sus formas isoméricas óptimamente activas o transformar las formas óptimamente activas en la forma racemica.

6) proceso de acuerdo a la reivindicación 5, caracterizado por llevar a cabo la hidrólisis selectiva en un medio alcohólico en la presencia de un hidróxido alcalino, preferiblemente hidróxido de potasio o sodio.

7) Composiciones farmacéuticamente que contienen con ingrediente activo uno o más compuestos de la fórmula general (I) -en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - o sus sales, solvatos, o isómeros óptimamente activos y las sales, solvatos de estos, en mezcla con uno o más excipientes utilizados en industria farmacéutica.

158

159

8) Composiciones farmacéuticamente de acuerdo con la reivindicación 7 que contienen como ingrediente activo uno o más compuestos de la fórmula general (IA) -en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X y n tienen los mismos significados como se definieron en la reivindicación 2 - o sus sales, solvatos, o isómeros óptimamente activos y las sales, solvatos de estos, en mezcla con uno o más excipientes utilizados en industria farmacéutica.

9) Composiciones farmacéuticamente de acuerdo con la reivindicación 8 que contienen como ingrediente activo uno o más compuestos de la fórmula (IV)

10) Uso de los compuestos de la fórmula general (I) - en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - en el tratamiento de enfermedades en el desarrollo de la cual el receptor A_3 juega un papel.

11) Uso de los compuestos de la fórmula general (I) - en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la

reivindicación 1 - de acuerdo a la reivindicación 10 como ligando A_3 en el caso de enfermedades del corazón, riñón, sistema respiratorio, sistema nervioso central, para la inhibición de la protección de la adenosina en el crecimiento de células tumorales, prevención de desgranulación de las células mástil, inhibición de la producción de citoquina, reducción de presión intraocular, inhibición de la liberación de TNFα, inhibición de eosinofilos, neutrofilos y otras células inmune, inhibición de broncoconstricción y la extravasación de plasma.

12) Uso de los compuestos de la fórmula general (I) - en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - de acuerdo a la reivindicación 10 y 11 como antagonistas de receptores A_3 en composiciones farmacéuticas y el mejoramiento antiinflamatorios, antiasmático, antiisquémicos, antidepresivos, antiarrítmicos, protectores renales, antitumorales, drogas antiparquinson y de mejoramiento cognitivo y en composiciones para el

160

161

tratamiento de daño por repercusión de miocardio, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de desetres respiratorio (ARDS) incluyendo bronquitis crónica, enfisema pulmonar o dispnea, reacciones alérgicas (por ejemplo rinitis, respuestas inducidas por hiedra venenosa, urticaria, escleroderma, artritis) otras enfermedades auto inmunes, enfermedad inflamatoria del intestino, enfermedad de Addison, enfermedad de Crohn, soriasis, reumatismo, hipertensión, desordenes de la función neurológica, glaucoma y diabetes como ingrediente activo.

13) Uso de los compuestos de la fórmula general (I) - en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - de acuerdo a la reivindicación 10, 11 y 12 como antagonistas de receptores A_3 para el tratamiento de enfermedades tales como asma, COPD y ARDS, glaucoma, tumor, enfermedades alérgicas e inflamatorias, isquemia, hipoxia, arritmia y enfermedades renales como ingrediente activo.

14) Uso del compuesto de fórmula general (IA) -en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X y n tienen el mismo significado como se definieron en la reivindicación 2 - en el tratamiento de enfermedades en el desarrollo de la cual el receptor A_3 juega un papel.

15) Uso de los compuestos de la fórmula general (IA) - en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X y n tienen los mismos significados como se definieron en la reivindicación 2 - de acuerdo a la reivindicación 13 como ligando A_3 en el caso de enfermedades del corazón, riñón, órganos respiratorio, sistema nervioso central, para la inhibición de la protección de la adenosina en el crecimiento de células tumorales, prevención de desgranulación de las células mástil, inhibición de la producción de citoquina, reducción de presión intraocular, inhibición de la liberación de TNFα, inhibición de eosinofilos, neutrofilos y otra migración de células inmune, inhibición de broncoconstricción y la extravasación de plasma.

162 163

16) Uso de los compuestos de la fórmula general (IA) - en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X y n tienen los mismos significados como se definieron en la reivindicación 2 - de acuerdo a la reivindicación 13, 14 como antagonistas de receptores A_3 en composiciones farmacéuticas antiinflamatorios, antiasmático, antiisquémicos, antidepresivos, antiarrítmicos, protectores renales, antitumorales, drogas antiparquinson y de mejoramiento cognitivo y en composiciones para el tratamiento o prevención de daño por repercusión de miocardio, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de desetres respiratorio (ARDS) incluyendo bronquitis crónica, enfisema pulmonar o dispnea, reacciones alérgicas (por ejemplo rinitis, respuestas inducidas por hiedra venenosa, urticaria, escleroderma, artritis) otras enfermedades auto inmunes, enfermedad inflamatoria del intestino, enfermedad de Addison, enfermedad de Crohn, soriasis, reumatismo, hipertensión, desordenes de la función neurológica, glaucoma y diabetes como ingrediente activo.

317) Uso de los compuestos de la fórmula general (I) - en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen los mismos significados como se definieron en la reivindicación 1 - de acuerdo a la reivindicación 14, 15 y 16 como antagonistas de receptores A_3 para el tratamiento de enfermedades tales como asma, COPD y ARDS, glaucoma, tumor, reacciones alérgicas, enfermedades inflamatorias, isquemia, hipoxia, arritmia y enfermedades renales.

18) Compuesto de fórmula general (II) -en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado como se definieron en la reivindicación 1

19) Compuesto de fórmula general (III) -en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado como se definieron en la reivindicación 1, con la condición de que R^3 no puede representar un grupo fenil, y R^1 y R^2 representan un átomo de hidrógeno, n=1, X representa un grupo -NH-, R^4 y R^5 forman juntos un grupo 1, 3-butadienilo y R^6 representa un grupo ciano.

164

165

20) Compuesto de fórmula general (IV) -en donde R^4, R^5 y R^6 tienen el mismo significado como se definieron en la reivindicación 1.

A65 166

DERIVADOS DE AMINOQUINOLINA Y AMINOPIRIDINA Y SU USO COMO LIGANDOS A3 ADENOSINA

RESUMEN

Los compuestos de fórmula general (I), en donde R^4 y R^5 representan el átomo de hidrogeno o forman juntos un grupo 1,3-butadienilo, opcionalmente sustituido por un grupo metilenidioxi o uno o más grupos alquilo C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi o átomo de halógeno, son ligandos fuertes de receptor A_3 de adenosina preferiblemente antagonistas.

PATENT COOPERATION TREATY

166

167

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Case 881/PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/HU02/00048	International filing date *(day/month/year)* 29.05.2002	Priority date *(day/month/year)* 31.05.2001
International Patent Classification (IPC) or both national classification and IPC C07D215/48		
Applicant SANOFI-SYNTHELABO		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.11.2002	19.08.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stix-Malaun, E Telephone No. +49 89 2399-8057

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/HU02/00048

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7, 9-42	as originally filed
8	received on 16.06.2003 with letter of 27.05.2003

Claims, Numbers

1-20	received on 16.06.2003 with letter of 27.05.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/HU02/00048

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-17 (Industrial Applicability)

   because:

   ☒ the said international application, or the said claims Nos. 10-17 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,5,7,10-18
	No:	Claims	19,20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-9,18-20
	No:	Claims	

2. Citations and explanations

see separate sheet

III NON-ESTABLISHMENT

Claims 10-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992 (1992-06-22) Columbus, Ohio, US; abstract no. 255453f, GEWALD K. ET AL.: 'Simple synthesis of 2,3-diaminoquinoline-3-carbonitriles.' XP002214323 & J. PRAKT. CHEM/CHEM.-ZTG., vol. 334, no. 1, - 1992 pages 89-91, -& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1992:255453 XP002214325

D2: WO 95 11244 A (ZENECA LTD.) 27 April 1995 (1995-04-27)

D3: CHEMICAL ABSTRACTS, vol. 136, Columbus, Ohio, US; abstract no. 69693x, SARHAN, ABD EL-WARETH A. O. ET AL.: 'Synthesis, characterization and reactions of 2-deoxo-5-deazaalloxazines.' XP002214324 & BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 11, - 2001 pages 2993-2998, -& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 2001:845787 XP002214326

D4: EP-A-1 180 518 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 20 February 2002 (2002-02-20)

D5: Beistein abstract (containing BRN3690429 & Chem.Ber.,64,1931,21,26)

have been considered for the examination procedure.

D3 might become relevant prior art in the European phase.
D5 was not cited in the international search report. A copy of the document is appended hereto.

2. NOVELTY

The amendments of claims 19 and 20 are not acceptable due to the fact that no basis for the provisos could be found in the description or in the prior art. Apart from this the whole novelty destroying overlap has not been removed. The provisos consist of the following definitions: "R3 cannot stand for....cyclohexyl". The original disclosure does not contain said definition for R3 whereas R8 may denote cycloalkyl which has not been excluded. The same applies for the present defintion of X denoting NH which should have been excluded. No basis could be found for the proviso "R6 cannot stand for hydrogen, if R4 stands for hydrogen and R5 stands for 4-halogen".Apart from this said proviso does not exclude the compound of the Beilstein abstract (see D5).

Accordingly the analysis with respect to novelty reads as follows:

The subject-matter of the claims 19 and 20 is anticipated by D1 and D5. D1 discloses exemplified compounds which are covered by present formula (III) of claim 19 (see abstract D1).

The compound of D5 (see Beilstein Registry Number 3690429) is cited exemplary for countless novelty destroying compounds which fall under formula (IV) of claim 20.
Accordingly the presently claimed subject matter of claims 19 and 20 lacks novelty.

The structurally closest compounds of D2 (see p. 110 and p. 111, compounds 82 a and b) differ from the compounds according to claim 1 in the substituent in position 2. Accordingly,the compounds of claim 1 are rendered novel.

The compounds of D4 lack the linker X. In contrast to the applicant's point of view there does not exist any further difference between the application and D4: Z of D4 may denote a divalent acyclic carbon group (see for substituents D4,p. 16,l. 29-30 in combination with p.20 l.50-53,l.56-58),R2 may denote an aromatic group which corresponds to present R7. Therefore the substituents in ortho-position to the nitrogen of D4 and the present application form overlapping parts. 19a!

Exemplified compounds and claims which are directed to second medical indication appear to be novel (Article 33(2) PCT).

3. INVENTIVE STEP

The presently claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons:

(a)The problem of the present application may be seen in the provision of further pyridine derivatives which are useful as adenosine receptor ligands which show antagonistic effects and high selectivity for the A3 receptor and are therefore useful in the treatment of inflammatory diseases.

The closest state of the art for the present application is represented by D4.

The compounds of D4 are useful in the same pharmaceutical field as the present ones.
As already sated under item novelty the presently claimed compounds lack the linking group X.

X may represent inter alia CH2. The examples of D4 show the same selection as the present ones (see tables 1-6,p.59-64) and differ therefore in a methylene unit,only.

Thus,the present compounds can be seen as simply analogous to those of D4. It is therefore obvious for the skilled person to assume that the presently claimed compounds show the alleged activity.

The problem defined under item (a) has been solved in an obvious manner.

(b) Therefore the problem of the present application has to be seen in the provision of a novel process which exhibits unexpected effects in relation to the compounds of D4.

From the general description of test procedures in the description it is not clear which compounds actually have been tested. For comparative tests with the closest prior art it is necessary the compounds only differ in the distinguishing feature.

Accordingly,no solution has been provided to the problem as defined under item (b).

An inventive contribution is not detectable with respect to the process or the intermediates. In addition to that it appears that the compounds according to formula (IV) do not contain the essential technical feature.

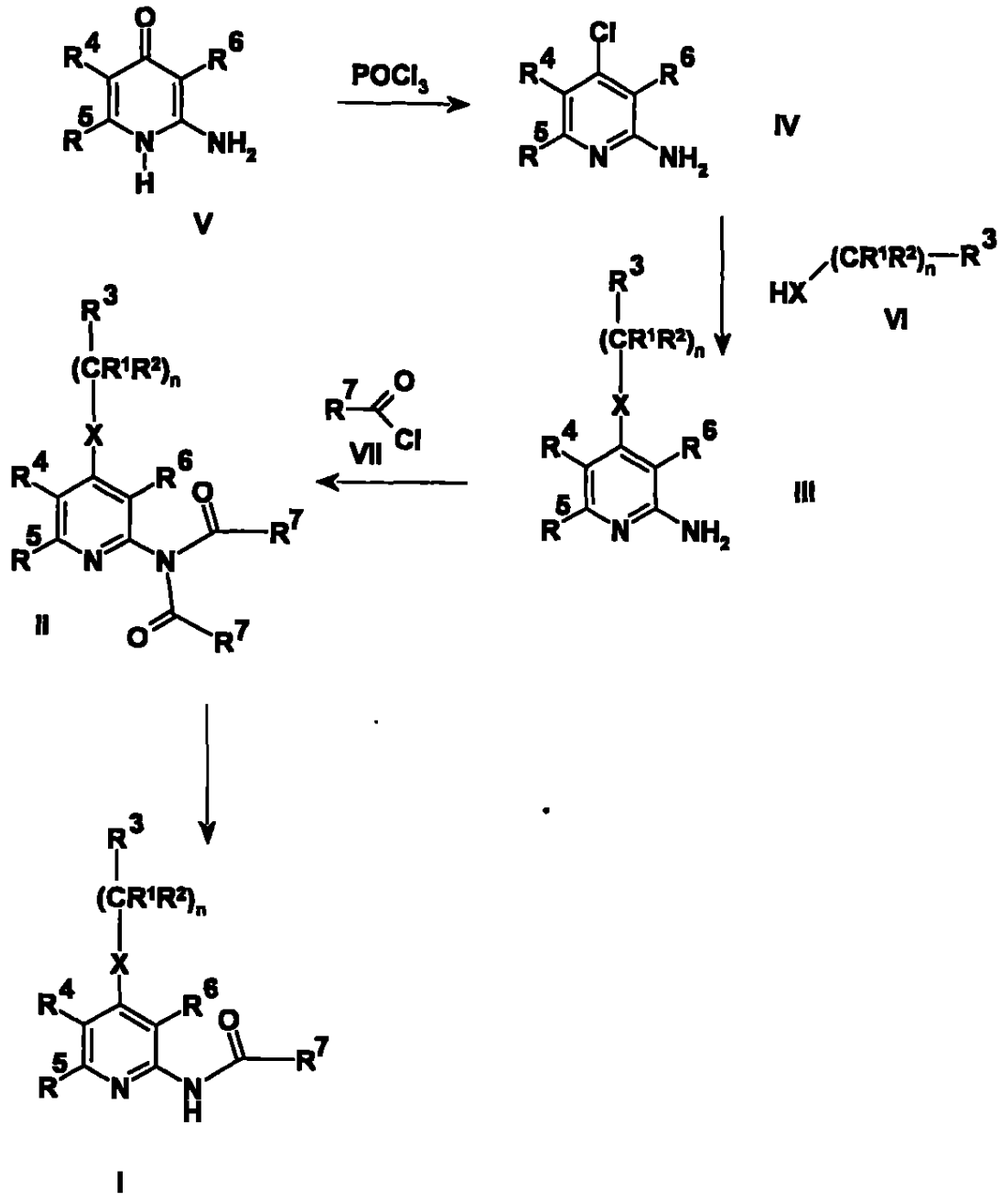
Accordingly inventive step cannot be acknowledged.

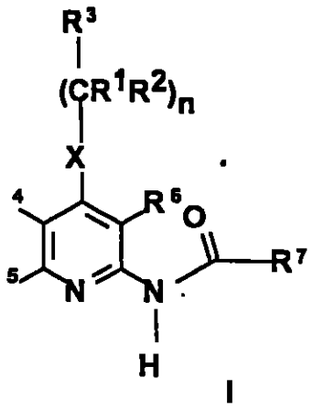
4. INDUSTRIAL APPLICABILITY

For the assessment of the present Claims 10-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Figure 6

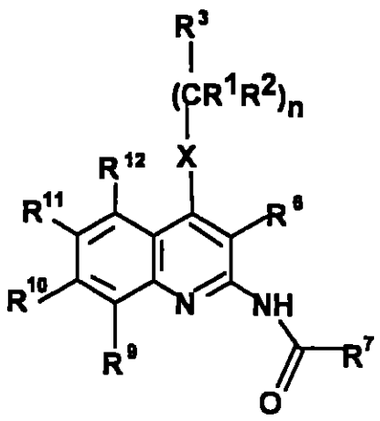
Reaction scheme 1.





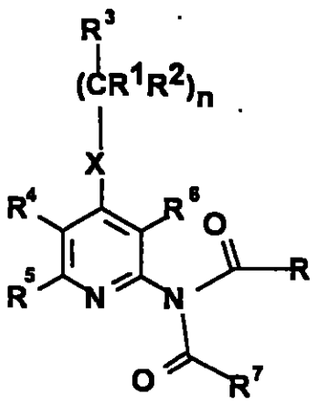
I

Figure 1



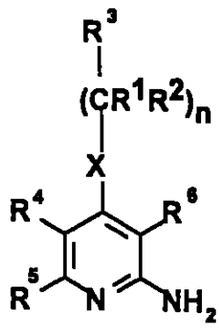
IA

Figure 2



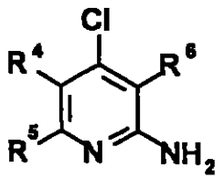
II.

Figure 3



III.

Figure 4



IV

Figure 5

daily dose is 1-100 mg active ingredient depending on the nature and severeness of the disease and on sex, weight etc. of the patient.

Further subject of the invention is the preparation of the compounds of the general formula (I) and of the intermediates of the general formulae (II) (III) and (IV).

The intermediates of the general formulae (II) (III) and (IV) which are used in the preparation process according to the invention, are partly novel. Substituents of the general formulae (II), (III) and (IV) have the meanings as defined above.

In the process according to our invention the bis-carboxamide of the general formula (II) is selectively hydrolysed and the resulting compound of the general formula (I) is, if desired, transformed into its salts, solvates or, liberated from its salt, solvate and separated into its geometric or optical isomers.

Substituents of the compounds of the general formula (I) may be transformed into each other by known methods.

Selective hydrolysis is performed by using alcoholic, preferably methanolic alkali hydroxide solution, preferably potassium and/or sodium hydroxide solutions, but other agents helping the hydrolysis of amides can also be used.

The selective hydrolysis can be carried out in a wide temperature range, favourably between 20 °C- 100 °C.

The compounds of the general formula (II) –wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are as defined above – can be obtained by several known methods, among them the one demonstrated in Scheme 1 (Figure 6), by acylation of the compounds of the formula (III), by using an acylation method known in the organic chemistry. For acylating agent preferably acyl chloride, for acid binding agent triethylamine and/or pyiridine can be applied, but other acid binding agents can also be used.

The compounds of the general formula (III) – wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n are as defined above – can be prepared from the compounds of the formula (IV) - by using methods known per se (Nan Zhang, Bioorg. and Med. Chem. Lett., 10, 2825, 2000).

The compounds of the general formula (IV) – wherein the meanings of R^4, R^5 and R^6 are as defined above – can be prepared from the compounds of the formula (V), by using methods known per se (D.L. Leysen, J. Heterocyclic Chem., 24, 1611, 1987).

Claims

1) Compounds of the general formula (I) - wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

X stands for a $-CH_2-$ group, -NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

AMENDED SHEET

2) Compounds of the general formula (IA) according to claim 1 - wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted with a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

X stands for a $-CH_2-$ group, -NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

AMENDED SHEET

3) Compounds of the formula (IA) according to claim 2, -wherein

R^1 stands for hydrogen atom or a methyl group;

R^2 stands for hydrogen atom or a methyl group;

R^3 stands for phenyl group, thienyl group or furyl group;

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or cyano group;

R^7 stands for 4-methoxyphenyl group, 3-methylphenyl group, 3-thienyl group or 3-furyl group;

X stands for –NH- group or oxygen atom and

n stands for 1-

and their salts, solvates and optically active isomers and their salts and solvates.

4) Compounds according to claims 1-3 as follows:

3-Methyl-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

4-Methoxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3-Methoxy- N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

N-(4-benzylamino-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

4-Methoxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)furan-2-carboxamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)thiophene-2-carboxamide

and their salts, solvates, optically active isomers and their salts and solvates.

5) Process for the preparation of a compound of the general formula (I), its salts, solvates, optically active isomers and their salts and solvates-wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1, characterized

by selective hydrolysis of a bis acid amide of the general formula (II) -wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1- and if desired transforming the substituens of the compound of the general formula (I) thus obtained in each other by methods known per se and/or transforming the compound of the general formula (I) thus obtained into its salts, or solvates, or liberating it from its salts or solvates and/or separating it into its optically active isomeric forms or transforming the optically active forms into the racemic form

6) Process according to claim 5, characterized by carrying out the selective hydrolysis in an alcoholic medium in the presence of an alkali hydroxide, preferable potassium or sodium hydroxide

7) Pharmaceutical compositions containing as active ingredient one or more compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry.

8) Pharmaceutical compositions according to claim 7 containing as active ingredient one or more compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry

9) Pharmaceutical composition according to claim 8 containing as active ingredient one or more compound of claim 4.

10)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - in the treatment of diseases in development of which the receptor A_3 plays a role.

AMENDED SHEET

180 187

11)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claim 10 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition of the protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of intraocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

12) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claims 10 and 11 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis,

15) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - according to claim 13 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition or protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of the innocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

16) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - according to claims 13 and 14 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison`s disease, Crohn`s disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes as active ingredient.

17) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – according to claims 14, 15 and 16 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic reactions, inflammatory diseases, ischemia, hypoxia, arrhytmia and renal diseases.

18) Compounds of the general formula (II)- wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1.

AMENDED SHEET

19) Compounds of the general formula (III)-wherein R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n have the same meaning as defined in claim 1, with the proviso that R^3 cannot stand for phenyl group, if R^1 and R^2 stand for hydrogenatom, n=1, X stands for a –NH– group, R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano group, with the further proviso that R^3 cannot stand for hydrogenatom , methyl, ethyl, 4-methoxyphenyl or cyclohexyl group , if n=0 , X stands for a $-NR^8$ - group, R^8 stands for hydrogenatom or methyl group R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano group, and with the further proviso that R^3 cannot stand for hydrogenatom, if , n=0, X stands for a $-CH_2-$ group, R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano or amino-carbonyl group.

20) Compounds of the general formula (IV)- wherein R^4, R^5, and R^6 have the same meaning as defined in claim 1, with the proviso that R^6 cannot stand for hydrogenatom, if R^4 stands for hydrogwnatom and R^5 stands for a 4-halogenatom.

185 184

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* Case 881/PCT

Box No. I TITLE OF INVENTION
NEW COMPOUNDS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Teleprinter No.
Applicant's registration No. with the Office

State *(that is, country)* of nationality: FRANCE
State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

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Budapest, Bimbó út 216.
H-1026 Hungary

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY
State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

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☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

ABT 185

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BALÁZS, László
Dunakeszi, Madách u. 15.
H-2120 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BALOGH, Mária
Dunakeszi, Barátság u. 21.
H-2120 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BATA, Imre
Budapest, Frankel Leó u. 7.
H-1027 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BÁTORI, Sándor
Budapest, Rákóczi F. 268/A
H-1214 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

T.NAGY, Lajos
Budapest, István u. 47. II/14.
H-1078 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TÍMÁRI, Géza
Vecsés, Zöldfa u. 8.
H-2220 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOÉR, Kinga
Budapest, Vizimolnár u. 2.
H-1031 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FINANCE, Olivier
9, rue de Nazareth, Bat D
F-34090 Montpellier
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FRANCE

State *(that is, country)* of residence: FRANCE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

186 187

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KAPUI, Zoltán
Budapest, Etele 56/a.
H-1115 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MIKUS, Endre
Budapest, Ida u. 96.
H-1162 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SZAMOSVÖLGYI, Zsuzsanna
Budapest, Bajnok u. 7.
H-1063 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SZELECZKY, Gábor
Budapest, Iványka Pál u. 30.
H-1155 Hungary

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

URBÁN-SZABÓ, Katalin
Budapest, Szent László u. 158.
H-1131 Hungary

This person is:
- [ ] applicant only
- [x] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: HUNGARY

State *(that is, country)* of residence: HUNGARY

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [x] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	
☒ BB Barbados	☒ KE Kenya	☒ SD Sudan
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BY Belarus		☒ SI Slovenia
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☒ TN Tunisia
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	
☒ DE Germany	☒ LV Latvia	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☒ MD Republic of Moldova	☒ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☒ ES Spain		☒ VN Viet Nam
☒ FI Finland	☒ MN Mongolia	☒ YU Yugoslavia
☒ GB United Kingdom	☒ MW Malawi	☒ ZA South Africa
☒ GD Grenada	☒ MX Mexico	☒ ZM Zambia
☒ GE Georgia	☒ MZ Mozambique	☒ ZW Zimbabwe
☒ GH Ghana	☒ NO Norway	

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ ..... ☐ ..... ☐ .....

☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box IV:

ARÁNYI, Péter

BALÁZS, László

BALOGH, Mária

BATA, Imre

BÁTORI, Sándor

T.NAGY, Lajos

TÍMÁRI, Géza

BOÉR, Kinga

FINANCE, Olivier

KAPUI, Zoltán

MIKUS, Endre

SZAMOSVÖLGYI, Zsuzsanna

SZELECZKY, Gábor

URBÁN-SZABÓ, Katalin

For further applicants the address written in BOX No. IV is the special address to which correspondance should be sent.

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) (31.05.2001) 31 May 2001	P01 02279	HUNGARY		
item (2) (01.03.2002) 1 March 2002	P02 00774	HUNGARY		
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☒ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the International search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / European Patent Office .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

APT 192

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	9
description (excluding sequence listing part)	:	42
claims	:	7
abstract	:	1
drawings	:	2
Sub-total number of sheets	:	61
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form: see (b) below)*	:	
Total number of sheets	:	61

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒	fee calculation sheet	:
2. ☐	original separate power of attorney	:
3. ☐	original general power of attorney	:
4. ☒	copy of general power of attorney; reference number, if any:	:
5. ☒	statement explaining lack of signature	:
6. ☐	priority document(s) identified in Box No. VI as item(s):	:
7. ☐	translation of international application into *(language)*:	:
8. ☐	separate indications concerning deposited microorganism or other biological material	:
9. ☐	sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
	(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
	(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
10. ☐	other *(specify)*:	:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Budapest, 27 May 2002

For and on behalf of SANOFI-SYNTHELABO

Dr. György Mihályi Katalin Mármarosi

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

192 193

TRATADO DE COOPERACIÓN DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

Archivo de referencia del agente o solicitante

Caso 881/PCT

PARA ACCIÓN COMPLEMENTARIA

Ver Notificación de Reporte de Examen Preliminar Internacional (del PCT/IPEA/416)

Solicitud Internacional No.

PCT/HU02/00048

Fecha de presentación internacional *(día/mes/año)*

29.05.2002

Fecha de Prioridad *(día/mes/año)*

31.05.2001

Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC

C07D215/48

Solicitante

SANOFI-SYNTHELABO

193

194

1. Este Reporte de Examen Preliminar Internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se remite al solicitante de acuerdo con el Articulo 36.

2. Este REPORTE consiste de un total de 7 hojas, incluyendo esta hoja de portada.

☒ Este reporte también se acompaña por ANEXOS, es decir hojas de la descripción, reivindicaciones y/o dibujos que han sido corregidos y son la base para este reporte y/o hojas que contienen rectificaciones hechas antes a esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas de acuerdo con el PCT).

Estos anexos consisten de un total de 8 hojas.

3. Este Reporte contiene indicaciones relacionadas con los siguientes ítems:

194

195

I ☒ Base del Concepto

II ☐ Prioridad

III ☒ Concepto de sin fundamento con respeto a novedad, nivel inventivo y aplicabilidad industrial

IV ☐ Falta de unidad de invención

V ☒ Declaración motivada de acuerdo con la regla 66.2(a)(ii) con respeto a novedad, nivel inventivo o aplicabilidad industrial; las citaciones y explicaciones ayudan a dicha declaración

VI ☐ Ciertos documentos citados

VII ☐ Ciertos defectos en la solicitud internacional

VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la petición

21.11.2002

Fecha de terminación de este reporte

19.08.2003

Nombre y dirección de correspondencia de la autoridad examinadora preliminar

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Oficial Autorizado

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196

197

REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/HU02/00048

I. Bases del Reporte

1. Con respecto a los **elementos** de la solicitud internacional: (reemplazo de las hojas que han sido suministradas a la Oficina de recepción en respuesta a una invitación de acuerdo con el Artículo 14 se refieren a en este reporte como "presentadas originalmente" y no se anexan a este reporte ya que ellas no contienen correcciones (Reglas 70.16 y 70.17)):

Descripción, páginas:

1-7, 9-42	como se presentó originalmente
8	recibido en 16.06.2003 con carta de 27.05.2003

197

198

Reivindicaciones, Números:

1-20 recibido en 16.06.2003 con carta de 27.05.2003

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el que la solicitud internacional se presentó, a menos que se indique lo contrario de acuerdo con este ítem.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el siguiente idioma:

,que es:

☐ el idioma de una traducción suministrada para propósitos de búsqueda internacional (de acuerdo con la regla 23.1(b)).

☐ el idioma de publicación de la solicitud internacional (de acuerdo con la regla 48.3(b)).

☐ el idioma de la traducción suministrado para propósitos de examen preliminar internacional (de acuerdo con la regla 55.2 y/o 55.3).

198

198

3. Con respeto a cualquier **secuencia de ácido amino y/o nucleótido** descrito en la solicitud internacional, el concepto escrito se emitió sobre la base de la lista de secuencia:

- ☐ Contenida en la solicitud internacional en forma impresa
- ☐ Presentada junto con la solicitud internacional en forma legible por computador
- ☐ Suministrada posteriormente a esta Autoridad en forma escrita
- ☐ Suministrada posteriormente a esta Autoridad en forma escrita forma legible por computador
- ☐ La declaración de que el listado de secuencias escrito suministrado posteriormente no va más allá de la descripción en la solicitud internacional como se presentó se ha suministrado.
- ☐ La declaración de que la información registrada en forma legible por computador es idéntica al listado de secuencias escrito que se ha suministrado.

199

200

4. Las correcciones han dado como resultado la cancelación de:

☐	la descripción,	páginas:
☐	las reivindicaciones,	Nos.:
☐	Los dibujos,	hojas:

5. ☐ Este reporte ha sido emitido como si (algunas de) las correcciones no hubieran sido hechas, ya que ellas han sido consideradas que van más allá de la descripción como se presentó, como se indicó en la casilla complementaria (Regla 70.2(c)):

(Cualquier reemplazo de hojas que contengan dichas correcciones se debe referir de acuerdo al ítem 1 y anexadas a este reporte)

6. Observaciones adicionales, si es necesario:

III. Concepto de sin fundamento con respecto a novedad, nivel inventivo y aplicabilidad industrial

200

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1. Las preguntas de si la invención reivindicada parece ser novedosa, involucrar un nivel inventivo (no ser obvio), o ser aplicable industrialmente no se han examinado con respecto a:

☐ La solicitud internacional completa

☒ Las reivindicaciones Nos. 10 - 17

(aplicabilidad Industrial)

Porque:

☒ la dicha solicitud internacional, o las dichas reivindicaciones Nos. 10 - 17 se relacionan a la siguiente materia objeto que no requiere un examen preliminar internacional (especificar):

ver hoja separada

☐ la descripción, reivindicaciones o dibujos (elementos particulares indicados adelante) o dichas reivindicaciones Nos. Son tan no claras que ningún concepto que tenga sentido se puede formular (especificar):

201

202

☐ las reivindicaciones, o dichas reivindicaciones Nos. Son respaldadas tan inadecuadamente por la descripción que ningún concepto que tanga sentido se puede formular.

☒ ningún reporte de búsqueda internacional ha sido establecido para las dichas reivindicaciones Nos.

2. Un examen preliminar internacional significativo no puede ser llevado a cabo debido a la interrupción del listado de secuencias de ácido amino y/o nucleótido para ajustarse con el estándar suministrado para en el anexo C de las Instrucciones Administrativas:

☐ la forma escrita no ha sido suministrada o no se ajusta con el estándar.

☐ la forma legible por computador no ha sido suministrada o no cumple con los estándares.

V. Declaración motivada de acuerdo con el Artículo 35(2) con respeto a novedad, nivel inventivo o

902

203

aplicabilidad industrial; las citaciones y explicaciones ayudan a dicha declaración

1. Declaración

Novedad (N)

Si: Reivindicaciones 1,5,7,10-18

No: Reivindicaciones 19,20

Nivel inventivo (IS)

Si: Reivindicaciones

No: Reivindicaciones 1-20

Aplicabilidad Industrial (IA)

Si: Reivindicaciones 1-9,18-20

No: Reivindicaciones

2. Citaciones y Explicaciones

Ver hoja separada

203 204

REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL - HOJA SEPARADA

Solicitud Internacional No.
PCT/HU02/00048

III SIN FUNDAMENTO

Las reivindicaciones 10-17 relaciona la materia objeto considerada por esta autoridad a ser cubierto por las estipulaciones de la Regla 67.1(iv) PCT. Por consiguiente, no se formulará ningún concepto con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(i) PCT).

V. DECLARACIÓN MOTIVADA

1. TÉCNICA ANTERIOR

Los documentos citados en el Reporte de Búsqueda Internacional

204

205

D1: CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 junio 1992 (1992-06-22) Columbus, Ohio, US; Resumen no. 255453f, GEWALD K. ET AL.: "Simple synthesis of 2,3-diaminoquinolina-3-carbonitrilos". XP002214323 & J. PRAKT. CHEM/.-ZTG., vol. 334, no. 1, - 1992 páginas 89 - 91, -& DATABASE CAPLUS [ON LINE]CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; aceso a base de datos no. 1992:255453 XP002214325

D2: WO 95 11244 A (ZENECA LTD.) 27 abril 1995 (1995-04-27)

D3: CHEMICAL ABSTRACTS, VOL. 136, Columbus, Ohio, US; resumen no. 69693x, SARHAN, ABD EL-WARETH A. O. ET AL.: "Synthesis, characterization and reactions of 2-deoxo-5-deazaalloxazines".
XP002214342 & BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 11, - 2001 páginas 2993 - 2998, -& DATABASE CAPLUS [ON LINE] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; acceso a base de datos no. 2001: 845787 XP002214362

D4: EP-A-1 180 518 (TAKEDA CHEMICAL INDUSTRIES, LTD.) FEBRERO 20 2002 (2002-02-20)

205

206

D5: Resumen Beistein (contiene BRN3690429 & Chem. Ver., 64, 1931, 21, 26)

Han sido considerados para el procedimiento de examen.

D3 puede llegar a ser importante en la técnica anterior en la fase Europea.

D5 no fue citado en el reporte de búsqueda internacional. Una copia del documento se anexa a esto.

2. NOVEDAD

Las correcciones de las reivindicaciones 19 y 20 no son aceptables debido al hecho de que no se pudo encontrar bases para las estipulaciones en la descripción o en la técnica anterior. A parte de esto la novedad completa destruye el traslapo que no se ha removido. Las estipulaciones consiste de las siguientes definiciones: "R3 no puede estar para ... ciclohexilo". La descripción original no contiene dicha definición para R3 mientras que R12 puede

206

207

denotar cicloalquilo que no ha sido excluido. Lo mismo aplica para la presente definición de X que denota NITRÓGENO el cual debe haber sido excluido. No se ha podido encontrar ninguna base para lo estipulado ""6 no puede ser para hidrógeno, y R4 es para hidrógeno y R5 es para 4-halógeno". A parte de esto dicha estipulación no excluye el compuesto del resumen Beilstein (ver D5).

De acuerdo con esto el análisis con respecto a novedad se lee como sigue:

La materia objeto de las reivindicaciones 19 y 20 se anticipa por D1 y D5. D1 describe compuestos ejemplificados que están compuestos por la presente fórmula (III) de la reivindicación 19 (ver resumen D1).

El compuesto D5 (ver número de registro Beilstein 3690429) se cita ejemplarmente para compuestos destructores novedoso que caen bajo la fórmula (IV) de la reivindicación 20.

207

208

De acuerdo con esto la materia objeto reivindicada actualmente mediante las reivindicaciones 19 y 20 hace falta novedad.

Los compuestos más cercanos estructuralmente de D2 (ver p. 110 y p. 111, compuestos 82 a y b) difieren de los compuestos de acuerdo a la reivindicación 1 en el sustituyente en la posición 2. De acuerdo con esto, los compuestos de la reivindicación 1 se vuelven novedosos.

Los compuestos de D4 falta el ligador X. Encontraste al punto de vista del solicitante no existe ninguna diferencia adicional entre la solicitud y D4: Z de D4 puede denotar un grupo de carbón acíclico divalente (ver para los sustituyentes D4, p. 16, l. 29-30 en combinación con p. 20 l. 50-53, l. 56-58), R2 puede denotar un grupo aromático que corresponde al presente R7. Por lo tanto los sustituyentes en la posición orto al nitrógeno de D4 y la presente forma de solicitud traslapan partes.

208

209

Los compuestos ejemplificados y las reivindicaciones que se dirigen a la segunda indicación médica parecen ser novedosos (Artículo 33(2) PCT).

3. NIVEL INVENTIVO

La materia objeto reivindicada actual no cumple los requerimientos del artículo 33(3) PCT por las siguientes razones:

(a) El problema de la presente solicitud puede ser visto en la estipulación de derivados de piridina adicionales que son útiles como ligandos receptores de adenocina que muestran efectos antagonistas selectivos para el receptor A3 y son por lo tanto útiles en el tratamiento de enfermedades inflamatorias.

El estado más cercano de la técnica de la presente solicitud se representa por D4.

Los compuestos de D4 son útiles en el mismo campo farmacéutico como el presente.

209

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Como ya se estableció de acuerdo al ítem novedad los compuestos reivindicados actuales le falta el grupo ligando X.

X puede representar inter alia CH2. Los ejemplos de D4 muestran la misma selección como los presentes (ver tablas 1-6, p. 59-64) y difiere por lo tanto solo en una unidad de metileno.

Así, los presentes compuestos pueden ser vistos como análogos simples de aquellos de D4. Esto es obvio por lo tanto para una persona experta para asumir que los compuestos reivindicados actuales muestran la actividad allegada.

El problema definido de acuerdo al ítem (a) ha sido resuelto en una forma obvia.

(b) por lo tanto el problema de la presente solicitud ha sido la estipulación de un proceso novedoso que exhibe efectos inesperados en relación a los compuestos de D4.

210

211

A partir de la descripción general de los procedimientos de ensayo en la descripción no es claro que compuestos actualmente han sido ensayados. Para ensayos comparativos con la técnica anterior más cercana es necesario que los compuestos solo difieran en la característica distintiva.

De acuerdo con esto, no se ha suministrado solución al problema como se definió de acuerdo al ítem (b).

Una contribución inventiva no es detectable con respecto al proceso o a los intermedios. En adición a que parece que los compuestos de acuerdo a la fórmula (IV) no contienen las características técnicas esenciales.

De acuerdo con esto no se puede reconocer nivel inventivo.

4. APLICABILIDAD INDUSTRIAL

Para la evaluación de las presentes reivindicaciones 10-17 sobre la pregunta si ellas tienen aplicabilidad industrial, no existe criterio

211

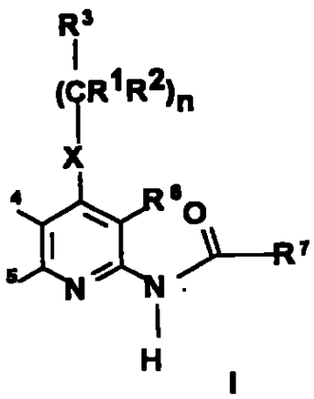
212

unificado en los estados contratantes del PCT. La patentabilidad también puede ser dependiente una vez la formulación de las reivindicaciones. El EPO, por ejemplo, no reconoce como aplicable industrialmente la materia objeto de las reivindicaciones a el uso de un compuesto en tratamiento médico, pero puede permitir, sin embargo, reivindicaciones a un compuesto conocido para primer uso en tratamiento médico y el uso de tal un compuesto para la fabricación de un medicamento para un tratamiento médico nuevo.

212

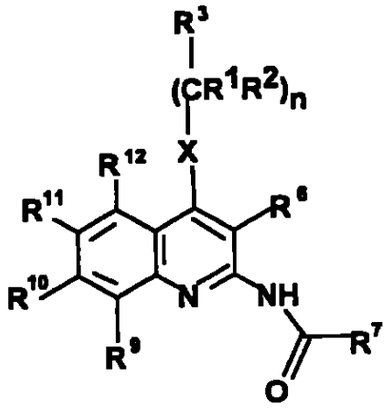
213

1/2



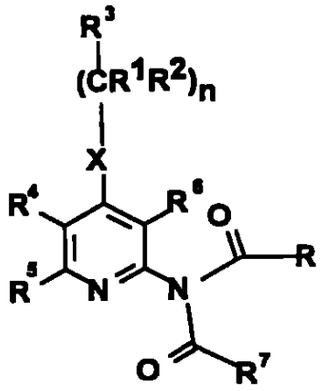
I

Figura 1



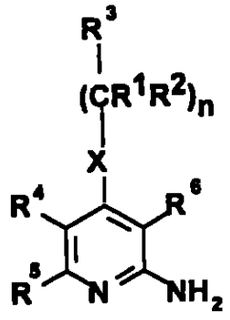
IA

Figura 2



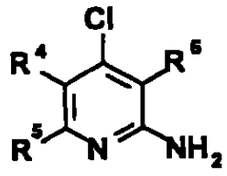
II.

Figura 3



III.

Figura 4



IV

Figura 5

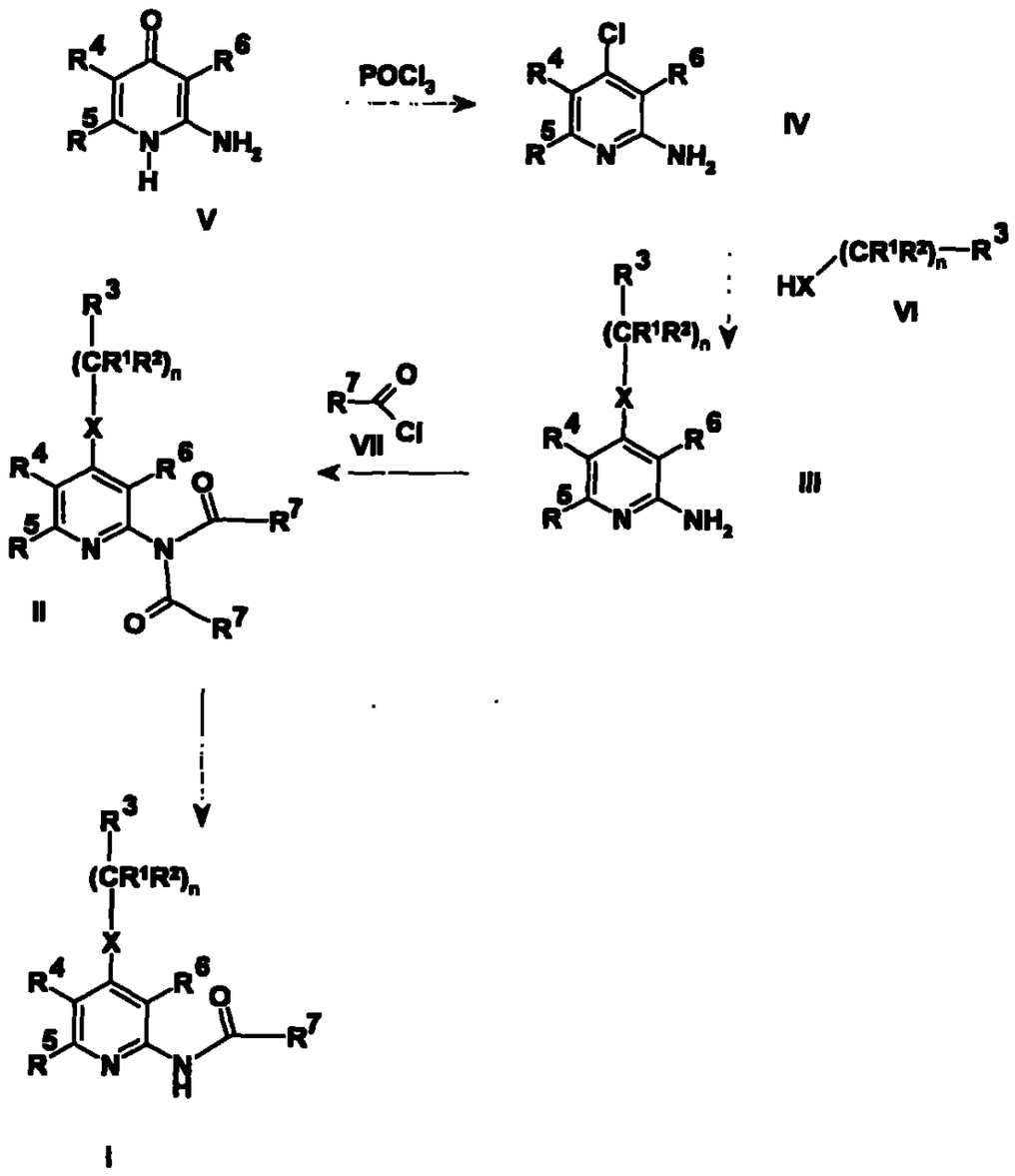
213

214

2/2

Figura 6

Esquema de Reacción 1.



Dosis diaria es 1-10 mg de ingrediente activo dependiendo de la naturaleza y la severidad y la enfermedad y en el sexo, peso etc. del paciente.

Un objeto adicional de la invención es la preparación de los compuestos de la fórmula general (I) y de los intermedios de fórmulas generales (II) (III) y (IV).

Los intermedios de las fórmulas generales (II) (III) y (IV) que son usados en el proceso de preparación de acuerdo con la invención, son parcialmente novedosos. Los sustituyentes de las fórmulas generales (II), (III) y (IV) tienen los significados según se definió anteriormente.

En el proceso de acuerdo con nuestra invención la bis-carboxamdia de fórmula general (II) es hidrolizada selectivamente y el compuesto resultante de la fórmula general (I) es, si se desea, transformada en sus sales, solvatos o liberada de sus sales, solvato y separada en sus isómeros geométricos u ópticos.

215

216

Los sustituyentes de los compuestos de la fórmula general (I) pueden ser transformadas en cada uno por métodos conocidos.

La hidrólisis selectiva es llevada a cabo una solución alcohólica preferiblemente de hidróxido de álcali metabólico, preferiblemente soluciones de potasio y/o hidróxido de sodio, pero otros agentes auxiliares de la hidrólisis de amidas también pueden ser usados.

La hidrólisis selectiva puede ser llevada a cabo en un rango amplio de temperaturas, favorablemente entre 20° C a 100° C.

Los compuestos de la fórmula general (II), en donde los significados de R^1, R^2, R^3, R^4, R^5, R^6, R^7, X y n son según se definió anteriormente, pueden ser obtenidos por diversos métodos conocidos, entre ellos el demostrado en el esquema 1 (figura 6), por acilación de los compuestos de la fórmula (III), usando un método de acilación conocido en la química orgánica. Como agente acilante preferiblemente el cloruro de acilo, como agente aglomerante ácido la trietilamina y/o piridina puede ser

aplicada, pero otros agentes aglomerantes ácidos también pueden ser usados.

Los compuestos de la fórmula general (III), en donde el significado de R^1, R^2, R^3, R^4, R^5, R^6, R^8 X y n son según se definió anteriormente, pueden ser preparados a partir de los compuestos de fórmula (IV), usando métodos conocidos per se (Nan Zhang, Bioorg, and Med. Chem. Lett., 10, 2825, 2000).

Los compuestos de la fórmula general (IV), en donde los significados de R^4, R^5, y R^6 son según se definió anteriormente, pueden ser preparados a partir de los compuestos de fórmula (V), usando métodos conocidos per se (D. L. Leysen, J. Heterocyclyc Chem., 24, 1611, 1987).

217

218

REIVINDICACIONES

1) Compuestos de fórmula general (I), en donde

R^1 es un átomo de hidrógeno o un grupo alquilo de cadena recta a ramificada con 1 a 4 carbonos;

R^2 es un átomo de hidrógeno o un grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos;

R^3 puede ser átomo de hidrógeno o grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos, o un grupo fenilo, grupo tienilo, o grupo furilo opcionalmente sustituido por uno o más grupos alquilo rectos o ramificados con 1 a 4 carbonos, grupos alcoxi con 1 a 4 carbonos o ramificados o un átomo halógeno, o para 1, 2 o 3 átomos nitrógeno o un átomo nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático de 5 o 6 miembros, opcionalmente sustituido por uno o más grupos alquilo de cadena recta o ramificada con 1 a 4

carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, o un átomo halógeno;

R^4 y R^5 son átomo de hidrógeno o forman juntos un grupo 1,3-butadienilo, opcionalmente sustituido por un grupo metilenedioxi o uno o más grupos alquilo de cadena recta o ramificada con 1 a 4 carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, grupo hidroxi o átomo halógeno;

R^6 es un átomo de hidrógeno o un grupo ciano, grupo aminocarbonilo, grupo alcoxicarbonilo con 1 a 4 carbonos o un grupo carboxi;

R^7 es un átomo de hidrógeno o grupo alquilo recto o ramificado con 1 a 4 carbonos, un grupo fenilo, grupo benzilo, grupo tienilo o grupo furilo, opcionalmente sustituido por un grupo metelenedioxi, o uno o más grupos alquilo de cadena recta o ramificada con 1 a 4 carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de

oxígeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático con cinco a seis miembros, opcionalmente sustituido por uno o más grupos alquilo de cadena recta o ramificada con uno a 4 carbonos, grupo alcoxi de cadena recta o ramificada con uno a cuatro carbonos, o átomo halógeno;

X es un grupo $-CH_2-$, grupo $-NH-$, grupo $-NR^8-$ o un átomo de azufre o un átomo de oxígeno o un grupo sulfa o un grupo sulfoxi, en donde R^8 es un grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos o un grupo cicloalquilo con 3 a 6 carbonos;

n es 0, 1 o 2-

y sus sales y solvatos, isómeros óptimamente activos y sus sales y solvatos.

2) Compuestos de fórmula general (1A) de acuerdo con la reivindicación 1, en donde

R^1 es un átomo de hidrógeno o un grupo alquilo de cadena recta a ramificada con 1 a 4 carbonos;

220

221

R^2 es un átomo de hidrógeno o un grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos;

R^3 puede ser átomo de hidrógeno o grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos, o un grupo fenilo, grupo tienilo, o grupo furilo opcionalmente sustituido por uno o más grupos alquilo rectos o ramificados con 1 a 4 carbonos, grupos alcoxi con 1 a 4 carbonos o ramificados o un átomo halógeno, o para 1, 2 o 3 átomos nitrógeno o un átomo nitrógeno y un átomo de oxigeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático de 5 o 6 miembros, opcionalmente sustituido por uno o más grupos alquilo de cadena recta o ramificada con 1 a 4 carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, o un átomo halógeno;

R^9, R^{10} y R^{11} son independientemente uno del otro átomo de hidrógeno o un grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, grupo hidroxi o átomo halógeno; o

221

222

R^9 y R^{12} son átomo de hidrógeno y R^{10} y R^{11} forman juntos un grupo metelenedioxi;

R^6 es átomo de hidrógeno o un grupo ciano, grupo aminocarbonilo, grupo alcoxicarbonilo con 1 a 4 carbonos, o grupo carboxi;

R^7 es un átomo de hidrógeno o grupo alquilo recto o ramificado con 1 a 4 carbonos, un grupo fenilo, grupo benzilo, grupo tienilo o grupo furilo, opcionalmente sustituido por un grupo metelenedioxi, o uno o más grupos alquilo de cadena recta o ramificada con 1 a 4 carbonos, grupo alcoxi de cadena recta o ramificada con 1 a 4 carbonos, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de nitrógeno y un átomo de oxígeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático con cinco a seis miembros, opcionalmente sustituido por uno o más grupos alquilo de cadena recta o ramificada con uno a 4 carbonos, grupo alcoxi de cadena recta o

222

223

ramificada con uno a cuatro carbonos, o átomo halógeno;

X es un grupo $-CH_2-$, grupo -NH-, grupo $-NR^8-$ o un átomo de azufre o un átomo de oxígeno o un grupo sulfa o un grupo sulfoxi, en donde R^8 es un grupo alquilo de cadena recta o ramificada con 1 a 4 carbonos o un grupo cicloalquilo con 3 a 6 carbonos;

n es 0, 1 o 2-

y sus sales y solvatos, isómeros óptimamente activos y sus sales y solvatos.

3) Compuestos de la fórmula (A) de acuerdo con al reivindicación 2, en donde

R^1 es átomo de hidrógeno o un grupo metilo;

R^2 es átomo de hidrógeno o grupo metilo;

R^3 es grupo fenilo, grupo tienilo o grupo furilo;

~~223~~ 224

R^9, R^{10}, R^{11}, o R^{12} son independientemente uno del otro átomo de hidrógeno, o un grupo alquilo recto o ramificado con 1 a 4 carbonos, grupo alcoxi recto o ramificado con 1 a 4 carbonos, grupo hidroxi o grupo halógeno; o

R^9 y R^{12} son átomo de hidrógeno y R^{10} y R^{11} forman juntos un grupo metilendioxi;

R^6 es un átomo de hidrógeno o un grupo ciano;

R^7 es un grupo 4-metoxifenil, grupo 3-metilfenil, grupo 3-tienil o grupo 3-furil;

X es un grupo -NH-o un átomo de oxígeno y

n es 1-

Y sus sales, solvatos e isómeros óptimamente activos y sus sales y solvatos.

4) Los compuestos de acuerdo con las reivindicaciones 1 a 3 como sigue:

224

225

3-metil-N-(4-benzilamino-3-ciano-quinilin-2-il)benzamida;

4-metoxi-N-(4-benzilamino-3-ciano-quinolin-2-il)benzamida;

3-metoxi-N-(4-benzilamino-3-ciano-quinolin-2-il)benzamida;

3,4-metilenedioxi-N-(4-benzilamino-3-ciano-quinolin-2-il)benzamida;

N-(4-benzilamino-3-ciano-quinolin-2-il)tiofeno-3-carboxamida;

N-(4-[2-tienilmetilamino]-3-ciano-quinolin-2-il)tiofeno-3-carboxamdia;

4-metoxi-N-(4-[2-tienilmetilamino]-3-ciano-quinolin-2-il]benzamida;

3,4-metilenedioxi-N-(4-[2-tienilmetilamino]-3-ciano-quinolin-2-il)benzamida;

N-(4-[2-furilmetilamino]-3-ciano-quinolin-2-il)furan-2-carboxamida;

N-(4-[2-furilmetilamino]-3-ciano-quinolin-2-il)tiofeno-2-carboxamida y sus sales, solvatos e isómeros óptimamente activos y sus sales y solvatos.

5) un proceso para la preparación de un compuesto de la fórmula general (I), sus sales,

225

226

solcitos, isómeros óptimamente activos y sus sales y solvatos, en donde en la fórmula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 X y n tienen el mismo significado que se definió en la reivindicación 1, caracterizado por la hidrólisis selectiva de una bisamida ácida de la fórmula general (II), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado que se definió en la reivindicación 1, y si la transformación deseada de los sustituyentes del compuesto de fórmula general (I) así obtenido en cada uno por métodos conocidos per se y/o transformar el compuesto de la fórmula general (I) así obtenido en sus sales, o solvatos liberándolo de sus sales o solvatos y/o separándolo en sus formas isoméricas óptimamente activas o transformar las formas óptimamente activas en formas racémicas.

6) El proceso de acuerdo con la reivindicación 5, caracterizado por llevar a cabo la hidrólisis selectiva en un medio alcohólico en la presencia de un hidróxido de álcali, preferiblemente hidróxido de potasio o de sodio.

226

227

7) las composiciones farmacéuticas que contienen como ingrediente activo uno o más compuestos de la fórmula general (I), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado de la reivindicación 1, o sus sales, solvatos o isómeros óptimamente activos y las sales, solvatos del mismo en mezcla con uno o más excipientes usados en la industria farmacéutica.

8) composiciones farmacéuticas de acuerdo con la reivindicación 7 que contiene como ingrediente activo uno o más compuestos de la fórmula general (IA), en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} X y n tienen el mismo significado de la reivindicación 2, o sus sales, solvatos o isómeros óptimamente activos y las sales y solvatos del mismos, y mezclas con uno o más excipientes usados en la industria farmacéutica.

9) La composición farmacéutica de acuerdo con la reivindicación 8 que contiene como

227

228

ingrediente activo uno o más compuestos de la reivindicación 4.

10) El uso de los compuestos de la fórmula general (I), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen le mismo significado definido en la reivindicación 1, en el tratamiento de enfermedades en desarrollo de los cuales el receptor A_3 juega un papel.

11) El uso de los compuestos de fórmula general (1), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1, de acuerdo con la reivindicación 10 como ligando A_3 en el caso de enfermedades del corazón, riñón, órganos respiratorios y sistema nervioso central, para la inhibición de la protección de adenosina en células de tumor crecientes, la prevención de la desgranulación celular, inhibición de la producción de citoquina, reducción de la prisión intraocular, inhibición de la liberación de TNFα, inhibición de la eucinófila, neutrófila y otras

migraciones de células inmune, la inhibición la broncoconstricción y la extravasación del plasma.

12) El uso de los compuestos de la fórmula general (I), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1, de acuerdo con las reivindicaciones 10 y 11 como antagonista receptor de A_3 en composiciones farmacéuticas que promueven la congmiscividad, antiinflamatorias, antiinstamínicos, antiesquémicos, antidepresantes, antiarrítmicos, protectores renales, antitumor, antiparkinson y en composiciones para el tratamiento y prevención de daños de repercusión miocardial, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de distensión respiratoria en adultos (ARDS) incluyendo bronquitis crónica, enfisema pulmonar o dismnea, reacciones alérgicas (por ejemplo rinitis, respuestas inducidas por veneno, urticaria), escleroderma, artritis, otras enfermedades autoinmune, enfermedades inflamatorias del intestino, enfermedad de Addison, enfermedad de Crohn, soriasis,

229

230

reumatismo, hipertensión, desorden de la función neurológica, glaucoma y diabetes como ingrediente activo.

13) El uso de compuestos de la fórmula general (I), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1, de acuerdo con las reivindicaciones 10, 11 y 12 como antagonista receptor de A_3 para el tratamiento de enfermedades tales como asma, COPD y ARDS, glaucoma, tumor, enfermedades alérgicas e inflamatorias, isquemia, hipoxia, arritmia y enfermedades renales como ingrediente activo.

14) El uso de los compuestos de la fórmula general (IA), en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X y n tienen el mismo significado según se definió en la reivindicación 2, en el tratamiento de enfermedades en desarrollo en los cuales el receptor A_3 juega un papel.

230
237

15) El uso de compuestos de fórmula general (IA), en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} X y n tienen el mismo significado según se definió en la reivindicación 2, de acuerdo con la reivindicación 13 como ligando de A_3 en el caso de enfermedades del corazón, riñones, órganos respiratorios y sistemas nervioso central para la inhibición o protección de la adenosina en células tumorales en crecimiento, prevención de la desgranulación de células mastoides, inhibición de la producción de citoquina, reducción de la presión intraocular, inhibición de la liberación de TNFα, inhibición de eucinófila, neutrófila y otras migraciones de células inmunes, inhibición de la broncoconstricción y extravasación del plasma.

16) Uso de los compuestos de la fórmula general (IA), en donde R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12} X y n tienen el mismo significado según la reivindicación 2, de acuerdo con las reivindicaciones 13 y 14 como antagonista de receptor de A_3 en composiciones farmacéuticas

antiinflamatorias, antiasmáticas, antiisquémicas, antidepresivas, antiarrítmicas, protectoras renales, antitumores, antiparkinson y de promoción congnoscitiva y en composiciones en el tratamiento o prevención de daños de repercusión miocardial, enfermedad pulmonar obstructiva crónica (COPD) y síndrome de distensión respiratoria en adultos (ARDS) incluyendo bronquitis crónica, enfisema pulmonar o dismnea, reacciones alérgicas (por ejemplo rinitis, respuestas inducidas por veneno, urticaria, escleroderma, artritis), otras enfermedades autoinmune, enfermedades inflamatorias del intestino, enfermedad de Addison, enfermedad de Crohn, soriasis, reumatismo, hipertensión, desorden de la función neurológica, glaucoma y diabetes como ingrediente activo.

17) Uso de los compuestos de la fórmula general (I) en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1, de acuerdo con las reivindicaciones 14, 15 y 16 como antagonista receptor de A_3 para el tratamiento de

enfermedades, COPD y ARDS, glaucoma, tumor, enfermedades alérgicas e inflamatorias, isquemia, hipoxia, arritmia y enfermedades renales.

18) Compuestos de la fórmula general (II), en donde R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1.

19) Compuestos de la fórmula general (III) en donde R^1, R^2, R^3, R^4, R^5, R^6, R^8, X y n tienen el mismo significado según se definió en la reivindicación 1, con la condición de que R^3 no puede ser un grupo fenilo, si R^1 y R^2 son un átomo de hidrógeno, n = 1, X es un grupo -NH-, R^4 y R^5 forman juntos un grupo 1,3-butadienilo y R^6 es un grupo ciano con la condición adicional de que R^3 no puede ser átomo de hidrógeno, metilo, etilo, 4-metoxifenilo, o grupos ciclohexilo, si n = 0, X es un grupo $-NR^8-$, R^8 es un átomo de hidrógeno o un grupo metilo, R^4 y R^5 forman juntos un grupo 1,3-butadienilo y R^6 es un grupo ciano, y con la condición adicional de que R^3 no puede ser átomo de hidrógeno si n = 0, X es un grupo -

CH_2-, R^4 y R^5 forman juntos un grupo 1,3-butadienilo y R^6 es un grupo ciano o amino-carbonilo.

20) Compuestos de la fórmula general (IV) en donde R^4, R^5, y R^6 tienen el mismo significado que se definió en la reivindicación 1, con la condición de que R^6 no puede ser átomo de hidrógeno, si R^4 es un átomo de hidrógeno y R^5 es un átomo 4-halógeno.

FORMATO DE DIGITALIZACION
RELACI N DE ANEXOS

Royal Technologies S.A.

235

Item	Expediente No	No de unidades	No de Folio ✓
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	✓
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Contiene Acta Final

FORMATO DE DIGITALIZACI N
RELACION DE ANEXOS

Royal Technologies S.A.

235

Item	Expediente No	No de unidades	No de Folio
1	CD		
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3	REVISTA		
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7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA	1	✓
9	SOBRE BLANCO TAMAÑO OFICIO		
10	OTROS:		

Observaciones: Contiene Arte Final

~~235~~ 236

SUPERINDUSTRIA Y COMERCIO

NIT : 800176089-2 Radicacion : [illegible] [illegible] Folios: [illegible]

Fecha (AMD): [illegible] [illegible]

Tramite : 411 PCT-PATENT [illegible] FASE NACI 411 PRESENTAC

Dependencia: [illegible] DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 03 - 85,510
FECHA : NOVIEMBRE 24 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	17923714	24/11/2003	28,427,550.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : ____________________

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.____________________

Cblo 12555-841-002-8

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	(✓)
- Indicación de que se solicita la concesión de una patente.	( )	(✓)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(✓)
- Descripción de la Invención.	( )	(✓)
- Dibujos de ser estos pertinentes.	( )	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA (✓) INCOMPLETA	( )	( )

DISEÑO INDUSTRIAL ( )

	USUARIO	RADICADOR
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que Incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

ESQUEMA DE TRAZADO ( )

	USUARIO	RADICADOR
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

237
238

Industria y Comercio
SUPERINTENDENCIA

Rad:03-107462
05/12/2003

03 107462 00

PETITORIO

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
Fecha ENTRADA EN FASE NACIONAL: 31/12/2003

1 **SOLICITUD DE:**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 **SOLICITANTE (71)**

Nombre: **SANOFI-SYNTHELABO** sociedad constituida y existente bajo las leyes de Francia.

Dirección: 174, avenue de France
F-75013, París
Francia.

Domicilio: París, Francia.

IDENTIFICACION

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐
Cual_____

Número: _____

3 **REPRESENTANTE O APODERADO**

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Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 38 11
Fax:: 217 92 11
E-mail: clientes@carvp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐
Cual_____

Número: 438.019 T.P. 31.929

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13-Gábor SZELECZKY
Ivánka Pál u. 30,,
Hungría.

14- Katalin URBÁN-SZANÓ
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Hungría.

5 **PCT (86)**
Solicitud Internacional No. PCT/HU02/00048 Fecha: 29 de mayo de 2002
Publicación Internacional No. WO 02/096879 A1 Fecha : 5 de diciembre de 2002

6 **Título (54)** DERIVADOS DE AMINOQUINOLINA Y AMINOPIRIDINA Y SU USO COMO LIGANDOS A3 ADENOSINA

7 Clasificación Internacional (51) C07D 215/48 A61K31/4706 239 238

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	HU.	31 de mayo de 2001	P01 02279
	HU.	1 de marzo de 2002	P02 00774

9 Comprobante de pago No.: 03 – 85.518 Fecha: 24 de noviembre de 2003

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por 400.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☒ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

149

239
240

REIVINDICACIONES

1) compuestos de la fórmula general (I)- en donde

R^1 representa átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado;

R^2 representa átomo de hidrógeno o grupo alquilo C_{1-4} recto o ramificado;

R^3 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante uno o más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de hidrógeno y un átomo de oxigeno o un átomo de nitrógeno y un átomo de azufre que contiene un anillo heteroaromático de 5 o 6 miembros, opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos alcoxxi C_{1-4} rectos o ramificados, o átomo de halógeno;

R^4 y R^5 representa átomos de hidrógeno o forma junto con el grupo 1, 3-butadienilo, opcionalmente sustituido mediante un grupo metilenedioxi o uno más grupos alquilos C_{1-4} rectos o ramificados, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi o átomo de halógeno;

R^6 representa átomo de hidrógeno o grupo ciano, un grupo aminocarbonilo, un grupo alcoxicarbonilo C_{1-4} o un grupo a carboxi;

R^7 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo benzilo, grupo tienilo, o grupo furilo, opcionalmente sustituido mediante un grupos metilenedixi o uno o más grupos alquilo C_{1-4} recto o ramificado, grupo alcoxi C_{1-4} recto o ramificado, grupo hidroxi, grupo trifluorometilo, grupo ciano o átomo de halógeno, o para uno, dos o tres átomos de nitrógeno o un átomo de hidrógeno y un átomo de oxigeno o un átomo de nitrógeno y un átomo de azufre que contienen anillos heteroaromáticos de 5 o 6 miembros, Opcionalmente sustituido mediante uno o más grupos alquilo C_{1-4} recto o ramificado, grupos

151

~~241~~ 242.

alcoxxi C_{1-4} rectos o ramificados, o átomo de halógeno;

X representa un grupo $-CH_2-$, grupo $-NH-$, grupo $-NR^8-$, o un átomo de azufre o un átomo de oxígeno o un grupo sulfo o un grupo sulfoxi- en donde R^8 representa un grupo alquilo C_{1-4} recto o ramificado o un grupo cicloalquilo C_{3-6}-;

n representa cero, 1 o 2- y sus sales, solvatos e isómeros óptimamente activos y sus sales , solvatos.

2) Compuestos de la fórmula general (IA) de acuerdo con la reivindicación 1- en donde

R^1 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado;

R^2 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado;

R^3 representa átomo de hidrógeno o un grupo alquilo C_{1-4} recto o ramificado, o un grupo fenilo, grupo

242
243

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado
Sanofi - Synthelabo.

Oficio N° 00519

ASUNTO:

Radicación N°	03-107462
Solicitud internacional	PCT/HU2002/00048
Fecha inicio fase nacional	31/12/2003
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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

DORIS ELENA POLO CORDOBA
Jefe (E) de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 13 ENE 2004.

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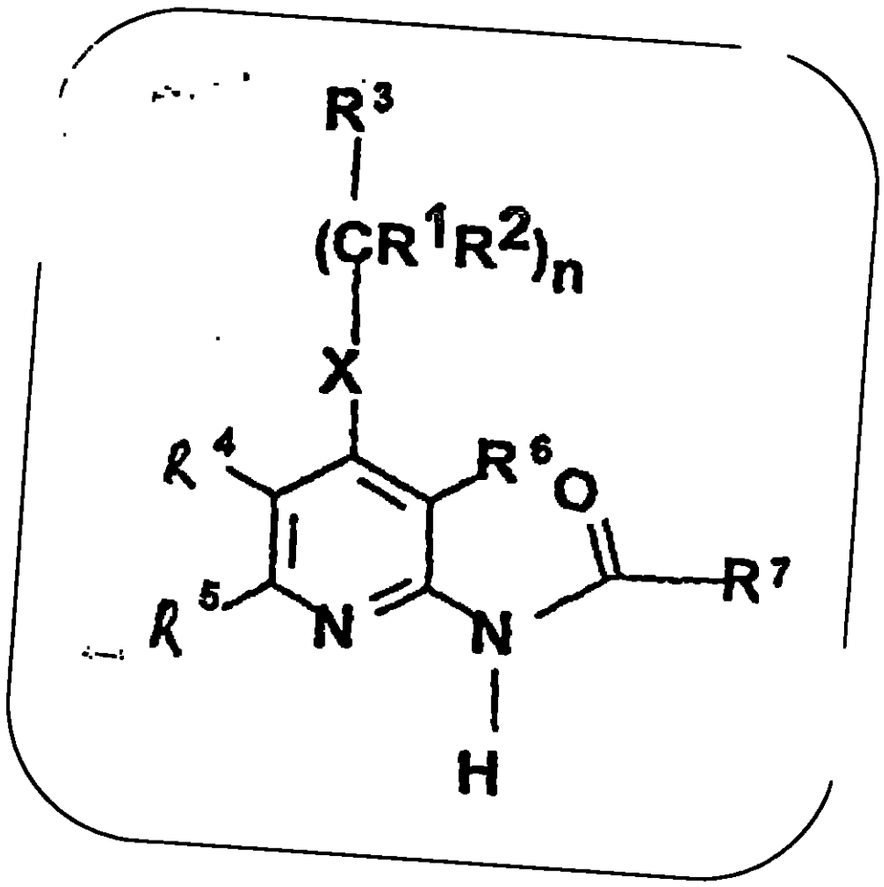
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