212

DIV NOR

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD

PATENTE DE INVENCIÓN

21. EXPEDIENTE Nº 03-79613

TÍTULO DERIVADOS ESPIROCICLICOS NUEVOS Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7

51. CLASIFICACIÓN INTERNACIONAL A61K31/527

71. SOLICITANTE WARNER-LAMBERT COMPANY LLC.

DOMICILIO 2001 Tabor Road, Morris Plains, NJ 07950, Estados Unidos de América

74. APODERADO CARLOS R. OLARTE

22. BOGOTÁ, D. C. SEPTIEMBRE 10, 2003

44 QF

(FORMA P 10)

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

03 079613 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03079613 00000000 Folios: 123
Fecha (AMD): 2003-09-10 17:06:57
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

cación

FORMULARIO ÚNICO 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: WARNER-LAMBERT COMPANY LLC.

Dirección: 2001 Tabor Road, Morrris Plains, NJ 07950 Estados Unidos de América.

Nacionalidad o Domicilio:

Lugar de Constitución: New Jersey; Estados Unidos de América.

Teléfono: Fax:

E-Mail

IDENTIFICACION

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre C, Calle 100 No. 8A-55 Piso 10.

Teléfono: 6386200 Fax: 6386201

E-Mail: filings@olarteraisbeck.com

IDENTIFICACION

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ]

Cual

Número 79.782.747 Bta TP 74.295

(4) INVENTOR (ES) (72)

Nombre: PATRICK BERNARDELLI, PIERRE DUCROT, EDWIGE LORTHIOIS, FABRICE VERGNE

Dirección: 146, RUE BOUCICAUT, F-94260, FRANCIA, 6 RESIDENCE D'AMBLAINVILLERS, F-91370 . VERRIERES LE BUISSON, 88 RUE D'ALLERAY, F-75015 PARIS, 1 ALLEE DU CHAMP DE LA MARE, CHEVRY II, F-91190 GIFSUR YVETTE FRANCIA

Nacionalidad o Domicilio: FRANCESA.

(5) PCT (85)

Solicitud Internacional No. PCT/EP02/03594 Fecha Marzo 18, 2002

Publicación Internacional No. WO 02/074754 Fecha Septiembre 26, 2002

(6) Título (54) DERIVADOS ESPIROCICLICOS NUEVOS Y SU USO COMO INHIBIDORES DE FOSFODIESTERASA-7

(7) Clasificación Internacional (51) A61K31/527

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EPO	Marzo 21, 2001	PCT/EP01/03355

(9) Comprobante de pago No. 61,690 **Fecha** 09-01-03

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional 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 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o titulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: BUSQUEDA INTERNACIONAL

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 74.782.747 de Btá T.P. 74.295

SUPERINDUSTRIA Y COMERCIO Folios: 123
Radicacion : 03079613 00000000
Fecha (AMD): 2003-09-10 17:06:57
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 61,690
FECHA : SEPTIEMBRE 1 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
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	14578066	29/08/2003	3,870,000.00

***** 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._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

WARNER- LAMBERT COMPANY LLC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

Sello: recibido el 21 julio de 2003 Departamento de Patentes NYD- Pfizer Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Secretario Asistente de Warner-Lambert Company LLC, con sede en Morris Plains, Nueva Jersey, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

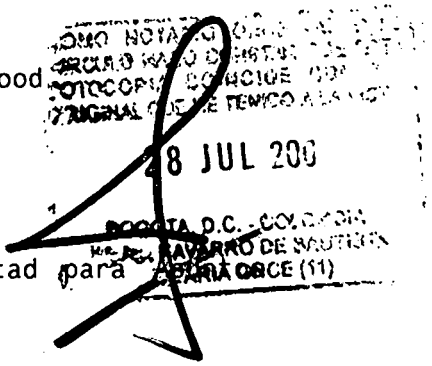
APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)
REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público 2.ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO 5. En Londres 6. El 17 de julio de 2003

7. Por el Secretario de Estado Principal de su Majestad para asuntos exteriores y de la mancomunidad.
8. No. G210433
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado



Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.
Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 199
Marlen Neira C.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

RECEIVED
JUL 21 2003
PFIZER INC.
PATENT DEPT. NYO

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Warner-Lambert Company LLC

domiciliado en

201 Tabor Road, Morris Plains, New Jersey 07950 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA

[redacted]

1937

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant Secretary of Warner-Lambert Company LLC

3. That Warner-Lambert Company LLC, having its principal place of business located in Morris Plains, New Jersey, U.S.A. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003
KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

COMO NOTARIO ... DE ESTE
TITULO MARGINAL CONSTITUYE UNA
FOTOCOPIA QUE COINCIDE CON EL
ORIGINAL QUE HE TENIDO A LA VISTA.
28 JUL 2003
BOGOTA, D.C. - COLOMBIA
MARIA MAVARRO DE BAUTISTA
NOTARIA ONCE (11)

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **K Greenwood**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

Certified/Attesté

5. at London/à Londres

6. the/le **17 July 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G210433**

9. Stamp:
   timbre:

FOREIGN AND COMMONWEALTH OFFICE LONDON

10. Signature: **R. Bawden**

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

NOTARIO
COPIA
28 JUL
BOGOTA D.C. - COLOMBIA
NAVARRO DE BAUTISTA
(11)

TRATADO DE COOPERACION DE PATENTES

De: OFICINA INTERNACIONAL
Para: HIRSCH, Denise
Pfizer
Global Research and Development
Fresnes Laboratorios
3-9, rue de la Loge, B.P. 100
F-94265 Fresnes Cedex
Francia

NOTIFICACION DE UN REGISTRO DE CAMBIO
(Regla PCT 92bis.1 e Instrucciones Administrativas, Sección 422)
NOTIFICACION IMPORTANTE

Fecha de envío: 25 de abril de 2003
Referencia de Solicitante o Agente: 018318 (A475) TP
Solicitud Internacional: PCT/EP02/03594
Fecha de presentación internacional: 18 de marzo de 2002

1. Las siguientes indicaciones aparecieron en archivo con respecto a:
X el solicitante
_ el inventor
_ el agente
_ representante común

Nombre y Dirección:
WARNER-LAMBERT COMPANY
201 Tabor Road
Morris Plains, NJ 07950
Estados Unidos de América

Nacionalidad: US
Residencia: US

2. Por medio de la presente, la Oficina Internacional notifica al solicitante que el siguiente cambio ha sido registrado con respecto a:
_ la persona
X el nombre
_ la dirección
_ la nacionalidad
_ la residencia

Nombre y Dirección:
WARNER-LAMBERT COMPANY LLC
201 Tabor Road
Morris Plains, NJ 07950
Estados Unidos de América

Nacionalidad: US

Residencia: US

3. Observaciones adicionales, si dan lugar:

4. Una copia de esta notificación ha sido enviado a:
X la Oficina receptora
_ la Autoridad de Búsqueda Internacional
X la Autoridad Examinadora Preliminar Internacional
_ las Oficinas designadas involucradas
X las Oficinas elegidas
_ otros:

La Oficina Internacional de la OMPI
34, chemin des Colombettes
1211 Ginebra 20, Suiza

Funcionario:
Evelyne DURAND
Teléfono: (41-22) 338-8236

RECEIVED ON
19. MAY 2003
Patents, Fresnes PCT

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

HIRSCH, Denise
Pfizer
Global Research and Development
Fresnes Laboratories
3-9, rue de la Loge, B.P. 100
F-94265 Fresnes Cedex
France

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)
25 April 2003 (25.04.03)

Applicant's or agent's file reference
018318 (A475) TP

IMPORTANT NOTIFICATION

International application No.
PCT/EP02/03594

International filing date (day/month/year)
18 March 2002 (18.03.02)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
WARNER-LAMBERT COMPANY
201 Tabor Road
Morris Plains, NJ 07950
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
WARNER-LAMBERT COMPANY LLC
201 Tabor Road
Morris Plains, NJ 07950
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No. (41-22) 740.14.35

Authorized officer
Evelyne DURAND
Telephone No. (41-22) 338 8236

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 September 2002 (26.09.2002)

PCT

(10) International Publication Number
WO 02/074754 A1

(51) International Patent Classification[7]: C07D 239/70, 401/04, 403/04, A61K 31/527, A61P 29/00, C07D 405/12, 413/12, 401/12

(21) International Application Number: PCT/EP02/03594

(22) International Filing Date: 18 March 2002 (18.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP01/03355 21 March 2001 (21.03.2001) EP

(71) Applicant *(for all designated States except US)*: **WARNER-LAMBERT COMPANY** [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BERNARDELLI, Patrick** [FR/FR]; 146, rue Boucicaut, F-94260 Fresnes (FR). **DUCROT, Pierre** [FR/FR]; 6, résidence d'Amblainvillers, F-91370 Verrieres Le Buisson (FR). **LORTHIOIS, Edwige** [FR/FR]; 88, rue d'Alleray, F-75015 Paris (FR). **VERGNE, Fabrice** [FR/FR]; 1, allée du Champ de la Marc, Chevry II, F-91190 Gif Sur Yvette (FR).

(74) Agents: **HIRSCH, Denise** et al.; Pfizer, Global Research and Development, Fresnes Laboratories, 3-9, rue de la Loge, B.P. 100, F-94265 Fresnes Cedex (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

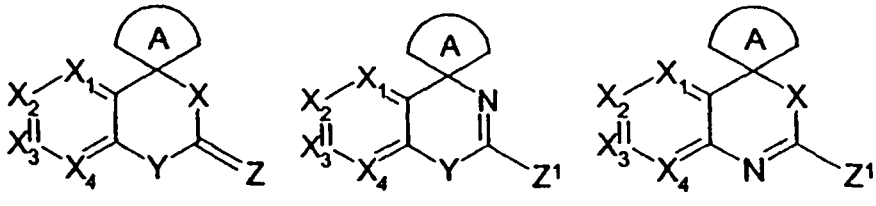
Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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

(54) Title: NEW SPIROTRICYCLIC DERIVATIVES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS



(I) (II) (III)

(57) Abstract: The invention provides compounds which are PDE7 inhibitors, having the following formula (I), (II) and (III), in which X_1, X_2, X_3, X_4, X, Y, Z, A and Z^1 are as defined in the description, methods for preparing them and their use for the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

WO 02/074754 A1

NEW SPIROTRICYCLIC DERIVATIVES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

Field of the invention.

The invention relates to spirotricyclic derivatives, the process for their preparation, and their use as phosphodiesterase 7 (PDE7) inhibitors.

Background of the invention.

Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, substrate specificity or sensitivity to cofactors or inhibitory drugs.

Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterization showed a high-affinity cAMP-specific PDE (Km=0.2 μM), that was not affected by cGMP potent selective PDE isoenzyme inhibitors.

PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway epithelial (AE) cell lines and several foetal tissues.

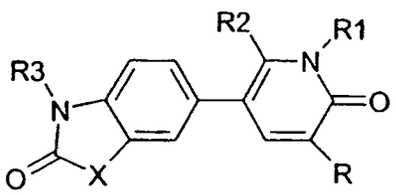
Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be devoid of the side effects associated with known selective PDE inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

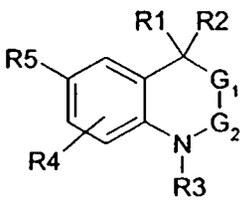
Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations, i.e. preferably nanomolar inhibitors.

WO 88/01508 discloses compounds of formula



where R is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, halo, cyano, carbamoyl, alkyl carbamoyl, formyl, alkylamino or amino;
X is –(CR4R5)a-NR6-(CR4R5)b-;
R1, R2, R3, and R5 are hydrogen or alkyl;
R4 and R6 are hydrogen, alkyl or aralkyl; a and b are 0, 1 or 2 and a + b = 0, 1 or 2; R4 and R5 groups on vicinal carbon atoms may together form a carbon-carbon double bond; and geminal R4 and R5 groups may together form a spiro substitutent, -(CH2)d-, where d is 2 to 5; or a pharmaceutically acceptable salt thereof. These compounds are described as cardiotonics.

WO 00/66560 discloses compounds of formula

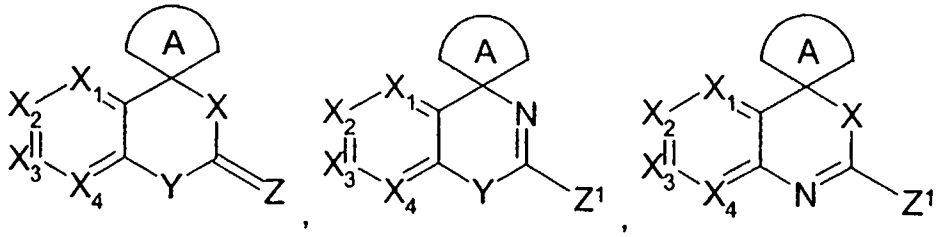


These compounds are described as progesterone receptor modulators

Summary of the invention.

The invention provides the use of spirotricyclic derivatives, which are PDE

inhibitors and more particularly PDE7 inhibitors, having the following formula (I), (II) or (III):



(I) (II) (III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;

    these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)$-NH-SO_2-CH_3, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
    - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O, S or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is N-R^{12} and Z is N-R^{13}, R^{12} and R^{13} may form together a -CH=N- group or a -C=C- group,
- when X is N-R^9 and Z is N-R^{13}, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

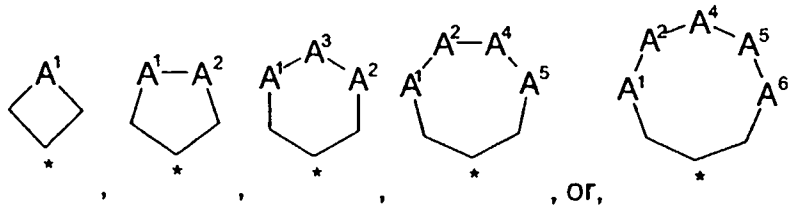
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , or,

in which,

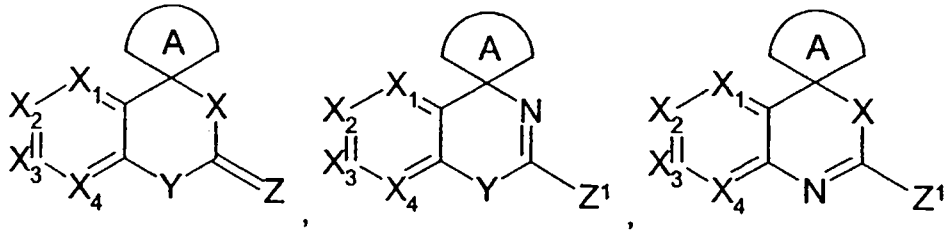
- A^1, A^2, A^3, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;

of their tautomeric forms, their racemic forms or their isomers and of their pharmaceutically acceptable derivatives,

for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

The invention also relates to compounds, which are PDE7 inhibitors, having the following formula (I), (II) or (III)



(I) (II) (III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, , the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

- R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)\text{-}NH\text{-}SO_2\text{-}CH_3$, NR^3R^4, $Q\text{-}R^2$, $Q\text{-}NR^3R^4$, $NR^2\text{-}Q\text{-}NR^3R^4$ or $NR^3\text{-}Q\text{-}R^2$ in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;

  these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)\text{-}NH\text{-}SO_2\text{-}CH_3$, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2, or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,

- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{10}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is N-R^{12} and Z is N-R^{13}, may form together a -CH=N- group or a -C=C- group,
- when X is N-R^9 and Z is N-R^{13}, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

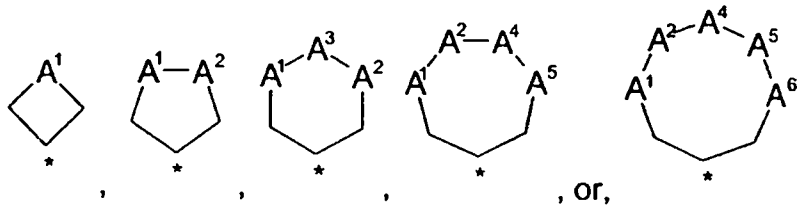
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , or,

in which,

- A^1, A^2, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- A^3 is selected from O, S, C, C(=O), SO or SO_2, or N-R^{18} when A^1 and/or A^2 are C(=O) or when Y is O or S, wherein R^{18} is as defined above;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$,

$COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,

R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that:

- not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;
- the cycle A does not contain more than 2 carbon atoms in an sp^2 hybridization state;
- when X is O, X_2 is not C-R^1 in which R^1 is
  - a thienyl substituted with CN or with CN and CH_3,
  - a phenyl substituted with CN, Cl, NO_2 or CN and F,
  - Br
  - F;

or their tautomeric forms, their racemic forms or their isomers and their pharmaceutically acceptable derivatives.

These compounds are selective PDE7 inhibitors. They can be used in the treatment of various diseases, such as T-cell-related diseases, autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS), allergy or inflammatory bowel disease (IBD).

The invention also relates to a process for preparing the above compounds.

The invention further concerns the use of a compound of formula (I), (II) or (III) for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

The invention also provides a method for the treatment of a disorder for which therapy by a PDE7 inhibitor is relevant, comprising administering to a mammal in need thereof an effective amount of compound of formula (I), (II) or (III).

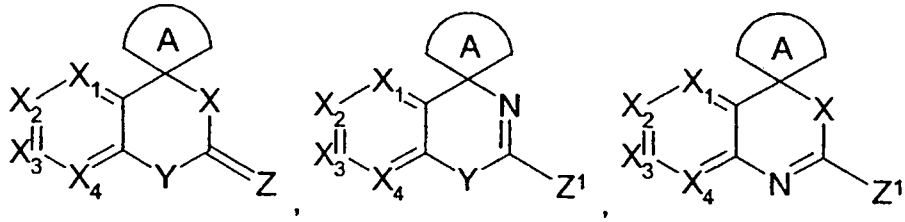
The invention also provides a method for the treatment of T-cell-related

diseases, autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS), allergy or inflammatory bowel disease (IBD), comprising administering to a mammal in need thereof an effective amount of compound of formula (I), (II) or (III).

The invention also concerns a pharmaceutical composition comprising a compound of formula (I), (II) or (III) together with a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

Detailed description of the invention.

The present invention provides the use of compounds, which are PDE7 inhibitors, having formula (I), (II) or (III),



(I) (II) (III)

in which

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkyl, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, , the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and

R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

- R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, $Q\text{-}R^2$, $Q\text{-}NR^3R^4$, $NR^2\text{-}Q\text{-}NR^3R^4$ or $NR^3\text{-}Q\text{-}R^2$ in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N or $(CH_2)_n$-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which n is an integer selected from 0, 1, 2, 3 or 4;
    these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, SO_3H, CH_3, SO_2CH_3, CF_3, $C(=O)\text{-}NH\text{-}SO_2\text{-}CH_3$, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,

- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X is O, S or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10} or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10} or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14} or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

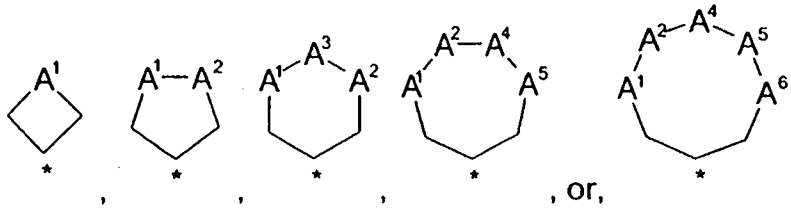
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14} or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , or,

in which,

- A^1, A^2, A^3, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:

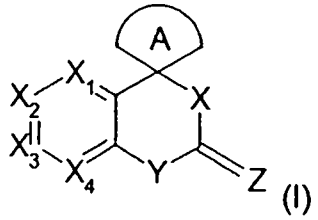
- hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
- lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;

of their tautomeric forms, their racemic forms or their isomers and of their pharmaceutically acceptable derivatives,

for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

A preferred use concerns the PDE7 inhibitors of formula (I),



(I)

in which X_1, X_2, X_3, X_4, X, Y, Z and A are as defined above,
for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

A more preferred use concerns the PDE7 inhibitors of formula (II) or (III) in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,
  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:

- halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,
- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

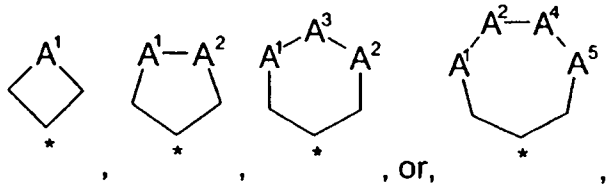
e) Z^1 is chosen from $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14} or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain,

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom;

for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

A particularly preferred use concerns the PDE7 inhibitors of formula (I), in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or

$C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:
  - halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$, $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
    - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,
    - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with,
      - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

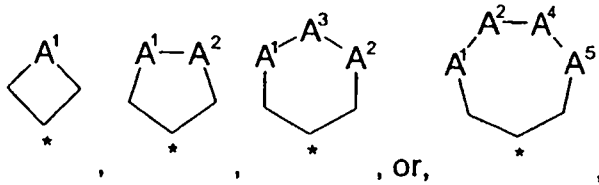
b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

e) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain,

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom;

for the prevention or the treatment of disorders for which therapy by a PDE7

inhibitor is relevant.

A preferred group of compounds of formula (II) or (III) are those in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:
  - halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
    - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

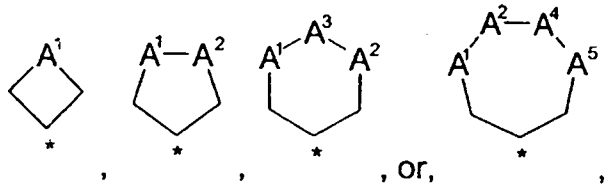
e) Z^1 is chosen from $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14},
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14} or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

A preferred group of compounds of formula (II) or (III) are the one in which X_1, X_2, X_3, X_4, X, Y, Z_1 and A are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

Another preferred group of compounds are compounds of formula (I) in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,

- lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, , the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
- R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N or $(CH_2)_n$-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which n is an integer selected from 0, 1, 2 or 3;

    these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, SO_3H, CH_3, SO_2CH_3, CF_3, C(=O)-NH-SO_2-CH_3, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or

two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X is NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10} or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with

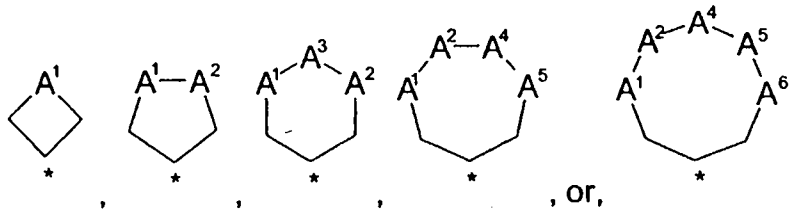
1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10} or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14} or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

e) A is a cycle chosen from:



, , , , or,

in which,

- A^1, A^2, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$,

$C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;

- A^3 is selected from O, S, C, C(=O), SO or SO_2, or N-R^{18} when A^1 and/or A^2 are C(=O) or when Y is O or S, wherein R^{18} is as defined above;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,

  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that:

- not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;
- the cycle A does not contain more than 2 carbon atoms in an sp^2 hybridization state.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3, X_4, X, Y, Z and A are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

Preferred compounds of formula (I) are those in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,

- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from:
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S or N, , the carbon atoms of these groups being unsubstituted or substituted with 1 or 2 groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N, or a bicyclic group,
      these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from:

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S or N or $(CH_2)_n$-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S or N, in which n is an integer selected from 0, 1, 2 or 3;

these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, CH_3, SO_2CH_3, CF_3, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

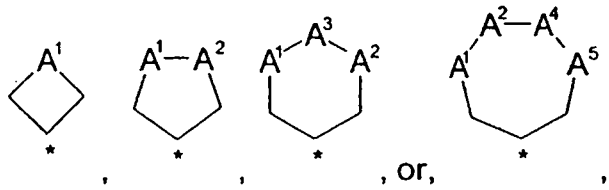
  R' and R'' together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X is NH;

c) Y is NH;

d) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^4 and A^5 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- A^3 is selected from O, S, C, C(=O), SO or SO_2, or N-R^{18} when A^1 and/or A^2 are C(=O) or when Y is O or S, wherein R^{18} is as defined above;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$ or $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent a heteroatom;

- the cycle A does not contain more than 2 carbon atoms in an sp^2 hybridization state.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3, X_4, X, Y, Z and A are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

More preferred compounds of formula (I) are those in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,
  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:

- halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with,
    - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
    - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
      - H, or,
      - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

    R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

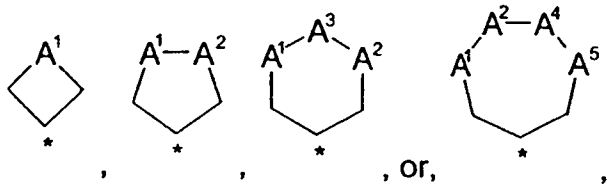
b) X_4 is $C\text{-}R^1$ in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

e) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3, X_4, X, Y, Z and A are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

Most preferred compounds of formula (I) are those in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, OR^2, in which R^2 is selected from hydrogen or lower alkyl;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

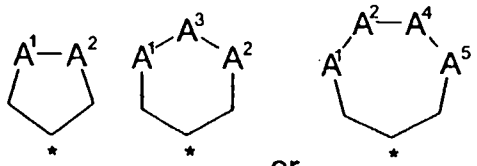
b) X_4 is C-R^1 in which R^1 is selected hydrogen, halogen, CH_3, CN, OR^2, in which R^2 is selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

e) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from carbon atoms, unsubstituted or substituted with CH_3;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain.

Preferably, X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X^5-R^5 in which,
  - X^5 is selected from :
    - a single bond,
    - a lower alkylene, optionally interrupted with 1 heteroatoms chosen from O, S and N
  - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group,

these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;
  - these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, CF_3, $C(=O)NH$-SO_2CH_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3 and X_4, are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

Preferably, X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 fluor atoms, OR^3, $COOR^3$ or NR^3R^4 in which R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl;

  R^3 and R^4 together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X^5-R^5 in which X^5 is a single bond and R^5 is selected from aryl, preferably phenyl, heteroaryl, preferably pyridyl, or a bicyclic group, preferably indolyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3,

in which Q1 and Q3 are the same or different and are selected from

- hydrogen, halogen, CN, lower alkyl,
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ or $SO_2NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl, Q4-heteroaryl in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 0, 1, 2 or 3;
    these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO_3H, $C(=O)-NH-SO_2-CH_3$, OR^6, $COOR^6$ or NR^6R^7, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,
- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3 and X_4, are as disclosed hereabove wherein when X_2 is $C-R^1$ and R^1 is X^5-R^5, then X^5 is not a single bond;

A preferred group of compounds is the group in which one of X_1, X_2, X_3 and X_4 is C-R^1 in which R^1 is hydrogen while the others are identical or different and are C-R^1 in which R^1 is selected from:

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X^5-R^5 in which,
  - X^5 is selected from :
    - a single bond,
    - a lower alkylene, optionally interrupted with 1 heteroatoms chosen from O, S and N
  - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower

alkyl, OR' or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;

- n is an integer selected from 0, 1, 2, 3 or 4;

- these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, CF_3, $C(=O)$-NH-SO_2-CH_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,

  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,

    - H, or,

    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

A preferred group of compounds of formula (I) is a group in which X_1, X_2, X_3 and X_4, are as disclosed hereabove wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond;

A preferred group of compounds is the group in which one of X_1, X_2, X_3 and X_4 is C-R^1 in which R^1 is hydrogen while the others are identical or different and are C-R^1 in which R^1 is selected from:

- Q1, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups halogen or with OR^3, $COOR^3$ or NR^3R^4 in which R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl;

  R^3 and R^4 together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X^5-R^5 in which X^5 is a single bond and R^5 is selected from aryl, preferably phenyl, heteroaryl, preferably pyridyl, or a bicyclic group, preferably indolyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3,

in which Q1 and Q3 are the same or different and are selected from

- halogen, CN, lower alkyl
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ or $SO_2NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl, Q4-heteroaryl in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 0, 1, 2 or 3;

    these groups being unsubstituted or substituted with 1or 2 groups selected from lower alkyl, CN, SO_3H, $C(=O)$-NH-SO_2-CH_3, OR^6, $COOR^6$ or NR^6R^7, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

A preferred group of compound is the group disclosed hereabove in which X^3 is C-R^1 in which R^1 is hydrogen.

Preferably, X_3 is C-R^1, in which R^1 is selected from :

- hydrogen or halogen, preferably Cl, or,
- X^5-R^5 in which R^5 is a single bond and R^5 is aryl, preferably phenyl or heteroaryl, preferably pyridyl, optionally substituted with one, two or three groups which are the same or different and which are selected from halogen, CN, CF_3, SO_2Me, OR^2, $COOR^2$, NR^2R^3, $SO_2NR^2R^3$ and $CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen and lower alkyl.

Preferably, X_3 is C-R^1, in which R^1 is selected from hydrogen or halogen, preferably Cl.

Preferably, X_3 is C-R^1 in which R^1 is hydrogen.

Preferably, X_4 is C-R^1, in which R^1 is selected from

- hydrogen, halogen, CF_3, O-lower alkyl, $COOR^2$ or,
- lower alkyl optionally substituted with OR^2, $COOR^2$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen and lower alkyl.

Preferably, X_4 is C-R^1, in which R^1 is selected from hydrogen, halogen, CF_3, methyl and methoxy.

Preferably, X_1 is C-R^1, in which R^1 is selected from

- hydrogen, halogen, preferably Cl or Br, OR^2, COR^2, $COOR^2$,$CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from
  - hydrogen,
  - lower alkyl, Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl;
    - n is an integer selected from 0, 1, 2 or 3;

  these groups being unsubstituted or substituted with lower alkyl, CN, C(=O)-NH-SO_2-CH_3, OR^6, SO_3H, $CONR^6R^7$, $COOR^6$, COR^6 or NR^6R^7,
  in which and R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2, COOH, OH ;
  R^6 and R^7 together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with ,
    - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
    - COR' or lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from hydrogen or lower alkyl;

- lower alkyl optionally substituted with CN, SO_3H, OR^3, NR^3R^4, $COOR^3$ or $CONR^3R^4$ in which R^3 and R^4 are the same or different and are selected from
  - hydrogen and,
  - lower alkyl optionally substituted with OH, COOH or NH_2

- the group X^5-R^5 in which X^5 is a lower alkylene optionally interrupted with a heteroatom selected from O and N and R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N and cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N,

these groups being unsubstituted or substituted OR^3 or $COOR^3$ in which R^3 is selected from hydrogen and lower alkyl;

R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- C(=O)-R' or a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from hydrogen or lower alkyl.

Preferably, X_1 is C-R^1, in which R^1 is selected from hydrogen, halogen, preferably Cl or Br, or OR^2 in which R^2 is selected from

- hydrogen,
- lower alkyl, unsubstituted or substituted with CN, C(=O)-NH-SO_2-CH_3, OR^6, SO_3H, $COOR^6$ or NR^6R^7,
- Q4-oxadiazole, Q4-tetrazole, Q4-morpholine, Q4-furan, Q4-isoxazole, in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 1 and 2;

these groups being unsubstituted or substituted with CH_3, OR^6 or $COOR^6$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2 or COOH.

Preferably, X_2 is C-R^1, in which R^1 is X^5-R^5, in which

- X^5 is a single bond,
- R^5 is phenyl or pyridyl,
  - optionally substituted with a lower alkyl, and,
  - substituted with $C(=O)NR^3R^4$ in which R^3 and R^4 together with the nitrogen atom to which they are linked, form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

Preferably, X_2 is $C\text{-}R^1$, in which R^1 is $X^5\text{-}R^5$, in which

- X^5 is a single bond,
- R^5 is phenyl,
  - optionally substituted with a methyl, and
  - substituted with $C(=O)NR^3R^4$ in which R^3 and R^4 together with the nitrogen atom to which they are linked, form a 6-membered heterocyclic ring, which may contain one or two nitrogen atoms, and which may be substituted with,
- a 6-membered heterocyclic ring, which may contain one or two nitrogen atoms and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,

- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;

In each of all the group of compounds defined above, the following substitutions are further preferred:

Preferably, compounds of the invention are compounds of formula (I).

Preferably, X is NH.

Preferably, Y is NH.

Preferably, Z is O.

Preferably, X is NH, Y is NH, and Z is O.

Preferably, A is selected from cyclohexyl or cycloheptyl, optionally interrupted with C(=O) or O, and unsubstituted or substituted with CH_3, OH or OCH_3.

Preferably, A is selected from unsubstituted cyclohexyl or cycloheptyl.

Preferably, A is unsubstituted cyclohexyl.

Preferably X is NH, Y is NH, Z is O and A is unsubstituted cyclohexyl.

Preferably X is NH, Y is NH, Z is O, A is unsubstituted cyclohexyl, X_3 is C-R^1 in which R^1 is hydrogen and X_4 is C-R^1, in which R^1 is selected from hydrogen, halogen, CF_3, methyl or methoxy.

In the following and in the foregoing text:

Halogen includes fluoro, chloro, bromo, and iodo. Preferred halogens are F and Cl.

Lower alkyl includes straight and branched carbon chains having from 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, isopropyl, tert-butyl and the like.

Lower alkenyl includes straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one double bond. Examples of such alkenyl groups are ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like.

Lower alkynyl includes straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one triple bond. Examples of such alkynyl groups are ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like.

Lower haloalkyl includes a lower alkyl as defined above, substituted with one or several halogens. A preferred haloalkyl is trifluoromethyl.

Aryl is understood to refer to an aromatic carbocycle containing between 6 and 10, preferably 6, carbon atoms. A preferred aryl group is phenyl.

Heteroaryl includes aromatic cycles which have from 5 to 10 ring atoms, from 1 to 4 of which are independently selected from the group consisting of O, S, and N. Preferred heteroaryl groups have 1, 2, 3 or 4 heteroatoms in a 5- or 6-membered aromatic ring. Examples of such groups are tetrazole, pyridyl, thienyl and the like.

Preferred cycloalkyl contain from 3 to 8 carbon atoms. Examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "interrupted" means that in a backbone chain, a carbon atom is replaced by an heteroatom or a group as defined herein. For example, in "cycloalkyl or cycloalkenyl optionally interrupted with C(=O) or with 1 heteroatom chosen from O, S, S(=O), SO_2 or N", the term "interrupted" means that C(=O) or a heteroatom can replace a carbon atom of the ring. Example of such groups are morpholine or piperazine.

Cycloalkenyl includes 3- to 10- membered cycloalkyl containing at least one double bond.

Heterocyclic ring include heteroaryl as defined above and cycloalkyl or cycloalkenyl, as defined above, interrupted with 1, 2 or 3 heteroatoms chosen from O, S, S(=O), SO_2, or N.

Bicyclic substituents refer to two cycles, which are the same or different and which are chosen from aryl, heterocyclic ring, cycloalkyl or cycloalkenyl, fused together to form said bicyclic substituents. A preferred bicyclic substituent is indolyl.

Sp^2 hybridization state: carbon atoms in an sp^2 hybridization state are trigonal instead of tetraedric. It means that the carbon atoms in a sp^2 hybridization state are linked to three atoms and form a double bond with one of these three atoms.

Preferred compounds are:

Spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
Spiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',7'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cyclobutane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromo-4-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one
8'-chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-thione

8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline

8'-Chloro-2'-methoxyiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline,

8'-Chloro-2'-dimethylaminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline],

8'-Chloro-1'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-1'-(ethoxycarbonylmethyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-Chloro-3'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-imidazo[2,1-b]quinazoline
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-[1,2,4]triazolo[3,4-b]quinazoline,
9'-Chlorospiro[cyclohexane-1-5'-(4',5'-dihydro)]-[1,2,4]triazolo[4,3-a]quinazoline,
Spiro[cyclohexane-1-9'-(8',9'-dihydro)-pyrazolo[4',3'-f]quinazolin]-7'(6'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-aminoethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8-Chloro-5-methoxyspiro[4H-benzo[d][1,3]oxazin-2-ylamine-4-4'-(tetrahydro-pyran-4'-yl)],
8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(ethoxycarbonylmethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

Among the compounds mentioned above, the following compounds are more preferred:

6'-Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromo-4-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one
8'-chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-thione
8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

Among the compounds mentioned above, the following compounds are more preferred:
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl] spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, and,

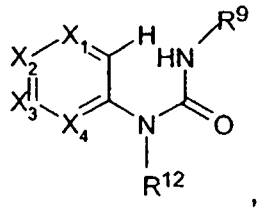
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,

8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

General process for the preparation of compounds of the invention

One method for preparing a compound of the formula (I) defined above in which Y is N-R^{12}, X is N-R^9 and Z is O comprises reacting a substituted urea of formula



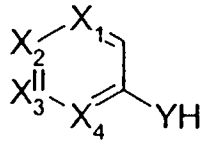
in which X_1, X_2, X_3, X_4, R_9 and R_{12} are as defined in the summary of the invention, with a cyclic ketone of formula



in which A is as defined in the summary of the invention, to obtain said compound of formula (I).

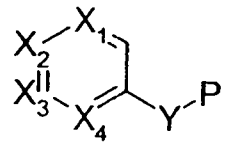
An alternative method for preparing a compound of formula (I) in which X is N-R^9, Y is O, S or NH, and X_1, X_2, X_3, X_4, A and R^9 are as defined in the summary of the invention and, comprises,

(1) reacting a compound (2a)



(2a)

in which X_1, X_2, X_3, X_4 are as defined in the summary of the invention and Y is O, S or NH, with a group P-LG in which P is a protecting group and LG is a leaving group to obtain compound (2b)

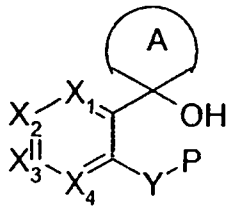


(2b)

(2) reacting compound (2b) with R-Li in which R is lower alkyl and then with a ketone of formula

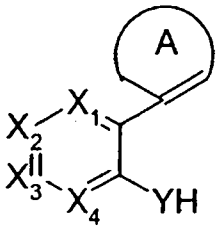


in which A is as defined in the summary of the invention to obtain compound (2c)



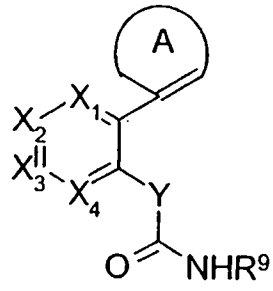
(2c)

(3) removing the protecting group P either under reductive conditions, acidic condition or basic condition to obtain compound (2d)



(2d)

(4) reacting compound (2d) with a group O=C=N-R^9 in which R^9 is as defined in the summary of the invention to obtain compound (2e)



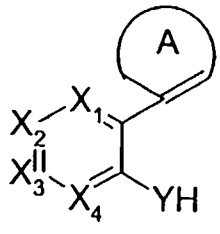
(2e)

(5) reacting compound (2e) with an acid to obtain said compound of formula (I),

(6) isolating said compound of formula (I).

An alternative process for the preparation of a compound of formula (I) in which X is O, S or NR^9, Y is O, S or NR^{12}, Z is O, S or NR^{13}, X_1, X_2, X_3, X_4, A, R^9, R^{12} and R^{13} are as defined in the summary of the invention and Y is O, S or NH, comprises,

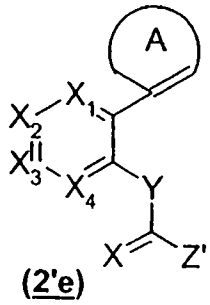
(1) reacting compound (2d)



(2d)

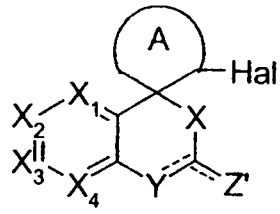
in which X_1, X_2, X_3, X_4 and A are as defined in claim 1,

with a group LG-C(=X)Z' or X=C=Z' in which LG is a leaving group, X is O, S or NR^9, Z' is OR, SR or NR^{13} in which R is lower alkyl or benzyl and R^9 and R^{13} are as defined in the summary of the invention, to obtain compound (2'e)



(2'e)

(2) reacting compound (2'e) with a source of halonium to obtain compound (2'f)



(2'f)

(3) reduction of compound (2'f) to obtain said compound of formula (I)

(4) optionally, when Z' is OR or SR, hydrolysis or hydrogenolysis of compound (2'f) is carried out to obtain compound said compound of formula (I) in which Z is O or S, and,

(5) isolating said compound of formula (I).

The compounds utilized in the invention include pharmaceutically acceptable derivatives of compounds of formula (I), (II) or (III) such as solvates, hydrates, pharmaceutically acceptable salts and polymorphs (different crystalline lattice descriptors).

Pharmaceutically acceptable salts of a compound of formula (I), (II) or (III) include salts having a basic part and salts having an acidic part.

The expression pharmaceutically acceptable salt of a compound of formula (I), (II) or (III) having a basic part should be understood to refer to the addition salts of the compounds of formula (I), (II) or (III) which may be formed from non-toxic inorganic or organic acids such as, for example, hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, fumaric and toluenesulfonic acid salts, and the like. The various quaternary ammonium salts of the derivatives (I), (II) or (III) are also included in this category of compounds of the invention. In addition, the expression pharmaceutically acceptable salt of a compound of formula (I), (II) or (III) having an acidic part is understood to refer to the usual salts of the compounds of formula (I), (II) or (III) which may be formed from non-toxic inorganic or organic bases such as, for example, the hydroxides of alkali metals and alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide. (See

also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, which is incorporated herein by reference.).

Use of a prodrug of a compound of the invention such as it would occur to one skilled in the art (see Bundgaard, *et al.*, Acta Pharm. Suec., 1987; **24**: 233-246), is also contemplated.

Pharmaceutical compositions.

The products of the invention are administered in the form of compositions, which are appropriate for the nature, and severity of the complaint to be treated. The daily dose in humans is usually between 1 mg and 1 g of product, which may be taken in one or more individual doses. The compositions are prepared in forms which are compatible with the intended route of administration, such as, for example, tablets, coated tablets, capsules, mouthwashes, aerosols, powders for inhalation, suppositories, enemas, foams (such as rectal foams) gels or suspensions. These compositions are prepared by methods which are familiar to those skilled in the art and comprise from 0.5 to 60% by weight of active principle (compound of the invention) and 40 to 99.5% by weight of a pharmaceutical vehicle or carrier which is appropriate and compatible with the active principle and the physical form of the intended composition.

Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders, tablets, cachets or encapsulated forms for capsules preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration. The drug may be delivered as a spray (either in a pressurized container fitted with an appropriate valve or in a non-pressurized container fitted with a metering valve).

Liquid form preparations include solutions, suspensions, and emulsions.

Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify. Enemas are obtained according to known procedures to prepare solutions adapted for rectal administration. Foams are prepared according to known methods (these foams can notably be similar to those used to administer a drug such as 5-ASA for treating rectocolite).

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of drug. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packaged tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Methods of treatment.

The compounds of the invention are PDE inhibitors, and particularly PDE7 inhibitors. These compounds have low IC_{50} values, typically at most 5 µM, preferably below 1 µM, and even below 100 nM.

It has been shown according to the invention that compounds of the invention are selective PDE7 inhibitors. "selective PDE7 inhibitors" refers to a compound which have an IC_{50} for PDE7 at least 5 times lower than the IC_{50} for a PDE distinct from PDE7, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times or 100 times lower than the IC_{50} value for a PDE distinct from PDE7.

A PDE distinct from PDE7 refers preferably to a PDE chosen from PDE1, PDE3, PDE4 or PDE5.

In particular, it has been shown according to the invention that the compounds of the invention, and more particularly the family of compounds given as examples in the present description, have an IC_{50} value for the enzyme PDE7 which is often 100 times lower than the value of their IC_{50} for a PDE distinct from PDE7, in particular PDE1, PDE3, PDE4 or PDE5.

Compounds of the invention can be used in the treatment of various diseases, as they can modulate inflammatory and immunological processes due to the increase of intracellular cAMP levels.

The diseases that can be treated are T-cell-related diseases, AE-cell-related diseases and immune disorders, such as autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, asthma, COPD, cancer, AIDS, inflammation, allergy and various inflammatory disorders such as, for example, inflammatory bowel disease (IBD).

The invention finally relates to a method for the treatment of the above-mentioned diseases comprising administering to a mammal, particularly a human, in need thereof an effective amount of compound of the invention.

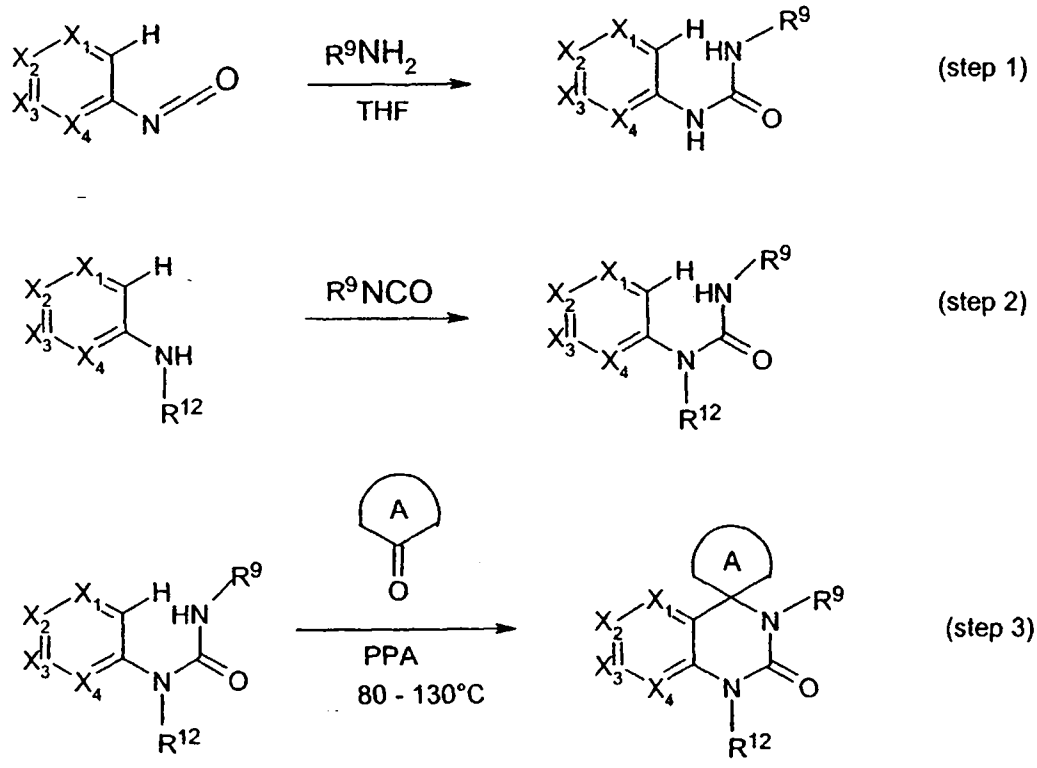
Processes for synthetising the compounds of general formula (I), (II) and (III)

The compounds according to the present invention can be obtained by carrying out several synthetic processes. Some of these synthetic processes (protocols A-L) are described below.

The solvent, reaction time, temperature, catalyst if any, can be varied in all steps described below for all routes, as the skilled man will appreciate.

Protocol A:

Scheme 1



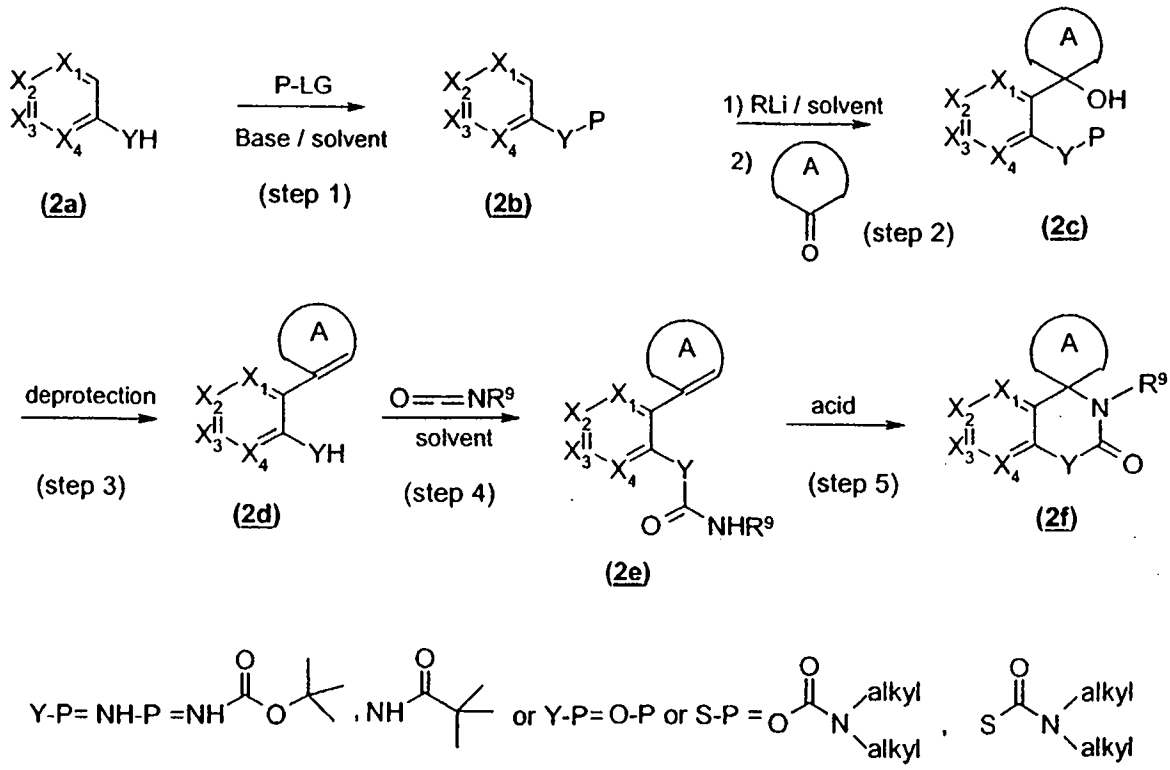
In scheme 1, X_1, X_2, X_3, X_4, A, R^9 and R^{12} are as defined in the summary of the invention.

The starting materials are either commercially available or can be prepared according to routes known to the skilled person. If the starting urea in step 3 is not commercially available, it can be prepared by treating the corresponding isocyanate with a primary amine in a solvent such as tetrahydrofuran (step 1) or treating the corresponding aniline with a substituted isocyanate in an organic solvent such as dichloromethane or acetonitrile (step 2).

In step 3, the urea is converted into the desired quinazolinone by reacting it with a cyclic ketone in polyphosphoric acid at 80-130°C.

Protocol B:

Scheme 2



In scheme 2, X_1, X_2, X_3, X_4, A and R^9 are as defined in the summary of the invention, Y may be O, S or NH and LG is a leaving group and R is lower alkyl.

The starting compounds are either commercially available or can be prepared according to routes known to the skilled person.

In step 1, compound (2a) is reacted with dialkyl-carbamoyl chloride to form the desired N,N dialkyl-carbamate or thiocarbamate according to routes known to the skilled person. See Poirier, M. ; Simard, M. ; Wuest, J.D. ; *Organometallics*, 1996, 15 (4), 1296-1300.

Other protecting groups may be used as oxygen-based directed metalation groups such as OMe, OMOM, $OP(OR_2)$, $OPO(NMe)_2$. See Snieckus, *Chem. Rev.*, 1990, 90, 879-933.

The aniline derivative is protected as a *t*-butyl carbamate or as a pivaloyl amide

according to routes known to the skilled person. See *Tet. Lett.*, 1994, 35(48), 9003-9006.

In step 2, compound (2b) is converted to a lithium salt (when Y is O or S) or to a dilithium salt thereof by reaction with an excess of lithium compound-forming agent such as *t*-butyllithium in a mixed solvent of anhydrous ether (for example, diethyl ether and tetrahydrofuran) and alkane (for example pentane), and reacted with an appropriate ketone. The reaction is carried out at low temperature (between –78 °C and 0°C) to give the expected tertiary alcool. The organolithium intermediate can also be formed by halogen-metal exchange. The organolithium can also be transmetallated into another organometallic reagent such as a cerate (with anhydrous cerium trichloride for example) prior to treatment with the ketone.

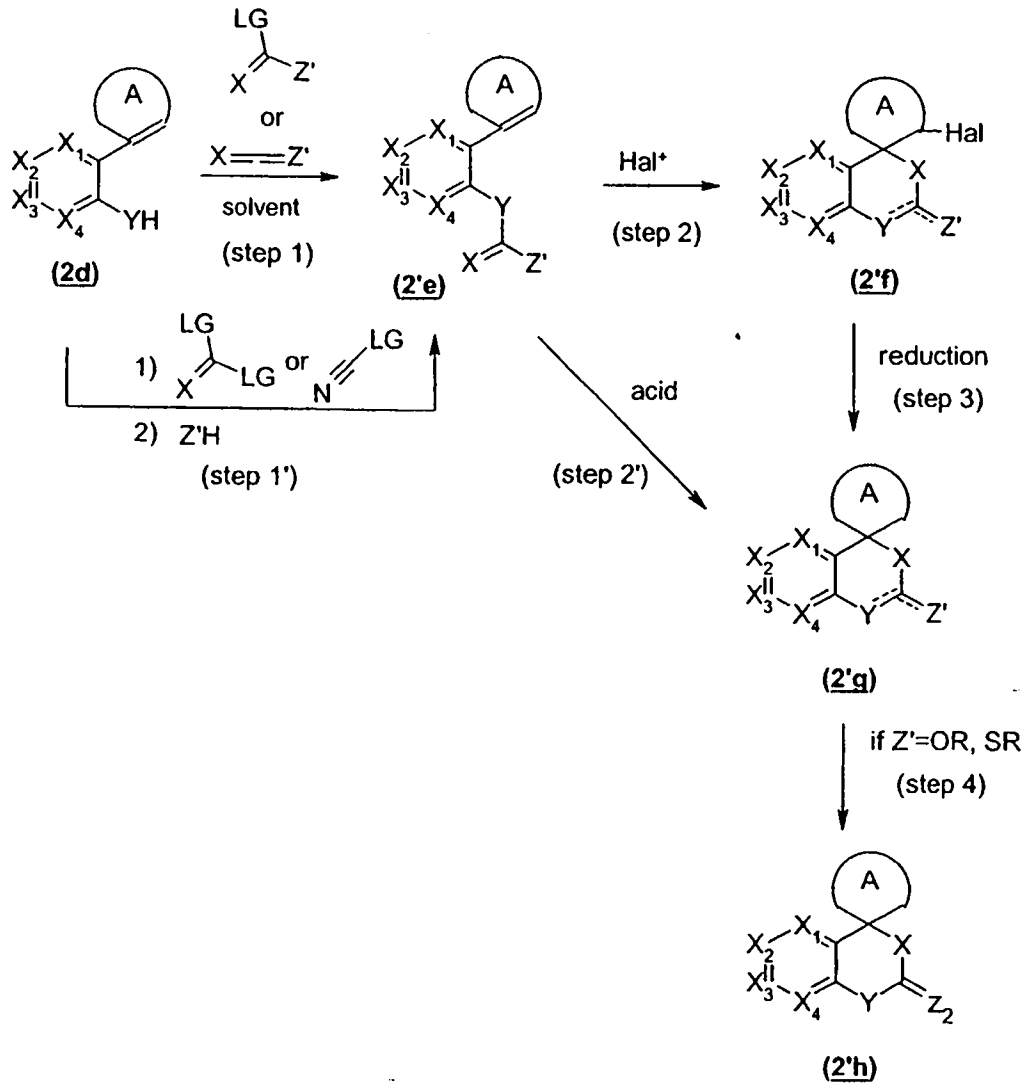
In step 3, the protecting group is removed according to routes known to the skilled person either under reductive conditions (when Y = O-P or S-P), under acidic condition or under basic condition to give compound (2d).

In step 4, compound (2d) is reacted with an appropriate substituted isocyanate to obtain compound (2e).

In step 5, treating compound (2e) with an acid (mineral acid or lewis acid) triggers cyclisation to give compound (2f).

Protocol B':

Scheme 2'



In scheme 2', X_1, X_2, X_3, X_4 and A are as defined in the summary of the invention, Y may be O, S or NR^{12}, X may be O, S, NR^9 and LG is a leaving group, Z' may be OR, SR, $NR^{16}R^{17}$ or NR^{13}, Hal is halogen, Z^2 may be O or S and where R^{12}, R^{13}, R^{16}, R^{17} and R^9 are as defined in the summary of the invention and R is alkyl or benzyl.

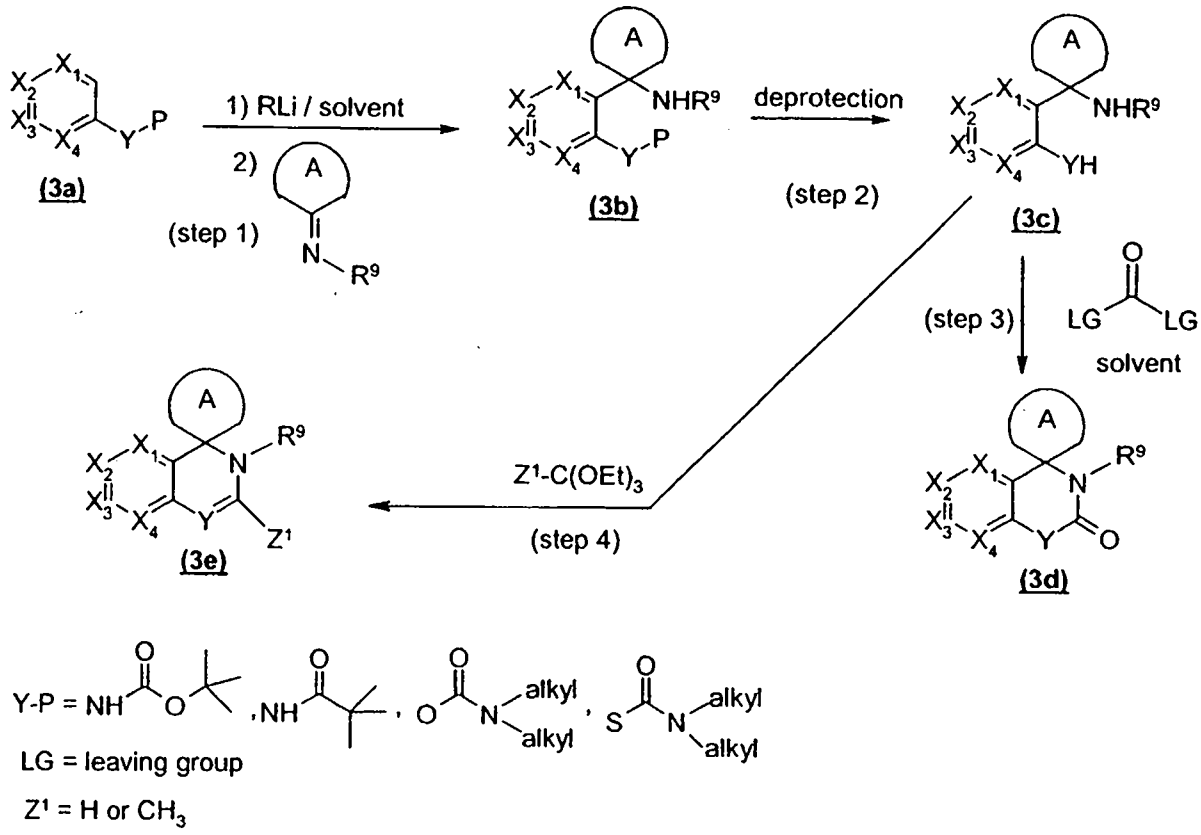
In step 1, intermediate **2d** obtained according to protocol B is reacted either with a carbonyl derivative such as a carbonate, a chloroformate, an isocyanate; a

thiocarbonyl derivative such as an isothiocyanate, a thionochloroformate, or others such as cyanamide, 3,5-dimethyl-1H-pyrazole-1-carboximidamide nitrate, S-methylisothiourea or equivalent. Alternatively, as shown in step 1', intermediate **2'e** can be prepared in two steps by treating **2d** with either cyanogens bromide or a carbonyl (or thiocarbonyl) derivative activated by two leaving groups such as phosgene (or thiophosgene), 1,1'-carbonyldiimidazole (or 1,1'-thiocarbonyldiimidazole), nitrophenylchloroformate or carbon disulfide, followed by addition of a nucleophile such as an amine, an alcohol or a thiol to introduce Z'. The appropriate reaction conditions for each route can be easily determined by the skilled person. When desired, certain intermediates **2'e** obtained can be derivatized into other intermediates **2'e** according to routes known to the skilled person. For instance, an intermediate thiourea **2'e** wherein Y=NH, X=S and Z'=NH_2 can be treated with an alkyl halide R-X according to reaction conditions known to the skilled person to give an intermediate **2'e** wherein Y=NH, X=NH and Z'=SR.

In step 2, intermediate **2'e** is treated with a source of halonium such as iodine, N-iodosuccinimide, bromine or N-bromosuccinimide to yield intermediate **2'f**. Similarly to **2'e**, intermediate **2'f** can be derivatized into different intermediates **2'f** according to routes known to the skilled person. The halide **2'f** can be reduced to **2'g** as shown in step 3 under reaction conditions known to the skilled person, such as treatment with trialkyl tin hydride and a radical initiator like azobisisobutyronitrile (AIBN) in an inert organic solvent. Alternatively, as shown in step 2', intermediate **2'e** could be directly transformed into **2'g** under acidic treatment according to conditions that can be determined by the skilled person. If necessary, intermediate **2'g** can also be derivatized into different **2'g** according to routes known to the skilled person. When Z' is OR or SR, intermediate **2'g** can be converted to **2'h** as shown in step 4. This can be done according to conditions known to the skilled person by hydrolysis under aqueous acidic media or by hydrogenolysis when R is benzyl.

Protocol C:

Scheme 3



In scheme 3, X_1, X_2, X_3, X_4 and A are as defined in the summary of the invention, R^9 is alkyl, aryl, alkylsulfonyl or arylsulfonyl, R is lower alkyl and Y may be O, S or NH.

An alternative method of preparing compound of the present invention is shown below and proceeds through the reaction of the organolithium intermediate with an imine.

In step 1, compound (3a) is converted to a lithium salt (when Y is O or S) or to a dilithium salt (when Y is NH) thereof by reaction with an excess of lithium compound-forming agent such as *t*-butyllithium in a mixed solvent of anhydrous ether (for example, diethyl ether and tetrahydrofuran) and alkane (for example pentane). The resulting organolithium is reacted with an appropriate imine at low temperature to give the expected tertiary amine (3b). The organolithium can also be transmetallated into another organometallic reagent such as a cerate (with

anhydrous cerium trichloride for example) prior to treatment with the ketone.

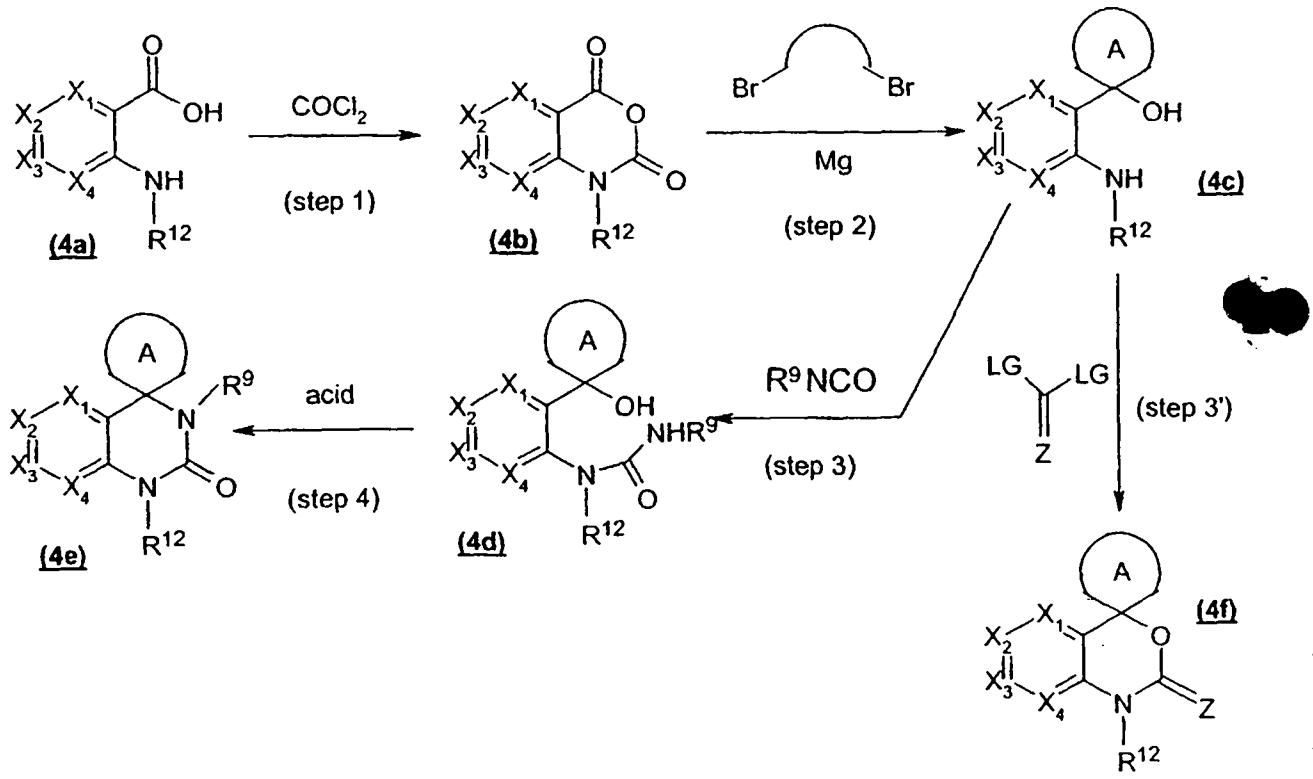
In step 2, the protecting group is removed according to routes known to the skilled person either under reductive conditions (when Y = O-P or S-P), under acidic condition or under basic condition to give compound (3c). When R^9 is alkyl or arylsulfonyl, this group can be deprotected into the NH derivative by reductive methods or hydrolysis according to methods known to the skilled person.

In step 3, compound (3c) is reacted with a compound selected from a carbonic acid halide such as phosgene a carbonic acid diester, 1,1'-carbonyldiimidazole and so on to obtain compound (3d).

In step 4, compound (3c) is reacted with an orthoester, in the presence of an acid to obtain compound (3e) or its tautomeric forms.

Protocol D :

Scheme 4



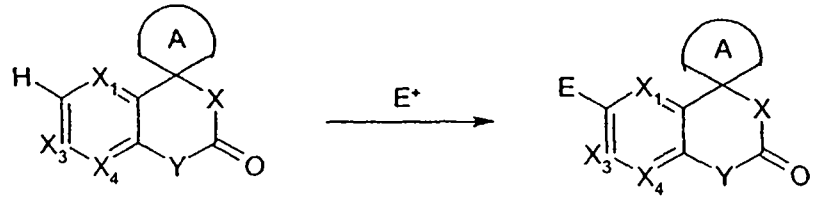
In scheme 4, X_1, X_2, X_3, X_4, A, R^9 and R^{12} are as defined in the summary of the invention, Z is O or S.

The starting materials are either commercially available or can be prepared according to routes known to the skilled person. In step 1, the starting anthranilic acid is treated with phosgene or an equivalent source of carbonyl such as triphosgene or carbonyl diimidazole. Various solvents and reaction conditions can be used and will be easily determined by the skilled person. The resulting isatoic anhydride is treated with the Grignard reagent obtained from a dihalide and magnesium in a solvent such as tetrahydrofuran or ether (step 2). In step 3, the aniline is converted to an urea by treatment with a substituted isocyanate. Various solvents and reaction conditions can be used and will be easily determined by the skilled person. For example, the reaction can be performed at room temperature or reflux in an inert solvent such as dichloromethane, acetonitrile or tetrahydrofuran in the presence or not of a base such as triethylamine or pyridine. In step 4, the resulting hydroxy-urea is subjected to an acid with or without an organic solvent. For example, the reaction can be carried out at 70-90°C in sulfuric acid. A solvent such as toluene or acetic acid may be added.

In step 3', compound 4c is converted to compound 4f by treatment with a carbonyl (or thiocarbonyl) derivative activated by two leaving groups such as phosgene (or thiophosgene), 1,1'-carbonyldiimidazole (or 1,1'-thiocarbonyldiimidazole).

Protocol E:

Scheme 5

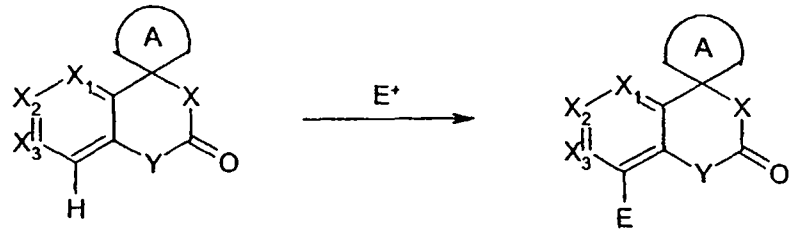


In scheme 5, X_1, X_3, X_4, X, Y and A are as defined in the summary of the invention.

The starting tricyclic compound is reacted with an electrophile E^+ such as halonium or acylium in presence or not of an activating agent in an organic solvent. Various solvents and reaction conditions for this aromatic electrophilic substitution can be used depending on the electrophile and will be easily determined by the skilled person. For instance, the starting material can be treated with a source of halonium such as N-iodo or N-bromosuccinimide in dimethylformamide at 60-70°C to give the corresponding halide. In another example, the starting material can be reacted with an acyl halide and aluminium trichloride, as Lewis acid, in a solvent such as dichloroethane at 80°C.

Protocol F:

Scheme 6

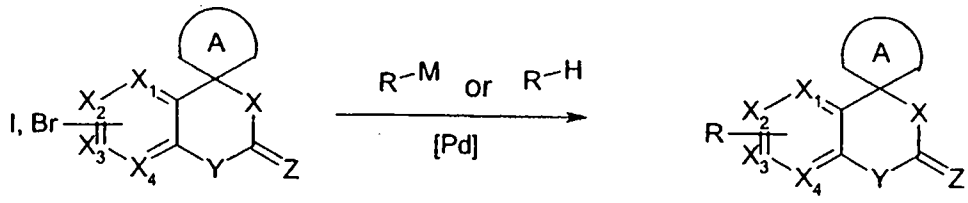


In scheme 6, X_1, X_3, X, Y and A are as defined in the summary of the invention and X_2 is not CH.

The starting tricyclic compound is reacted with an electrophile E^+ in presence or not of an activating agent in an organic solvent. This aromatic electrophilic substitution is similar to Protocol E except that in this case, since X_2 is different from CH, the substitution is oriented in position 8. Similarly to Protocol E, various solvents and reaction conditions for this aromatic electrophilic substituion can be used depending on the electrophile and will be easily determined by the skilled person.

Protocol G:

Scheme 7



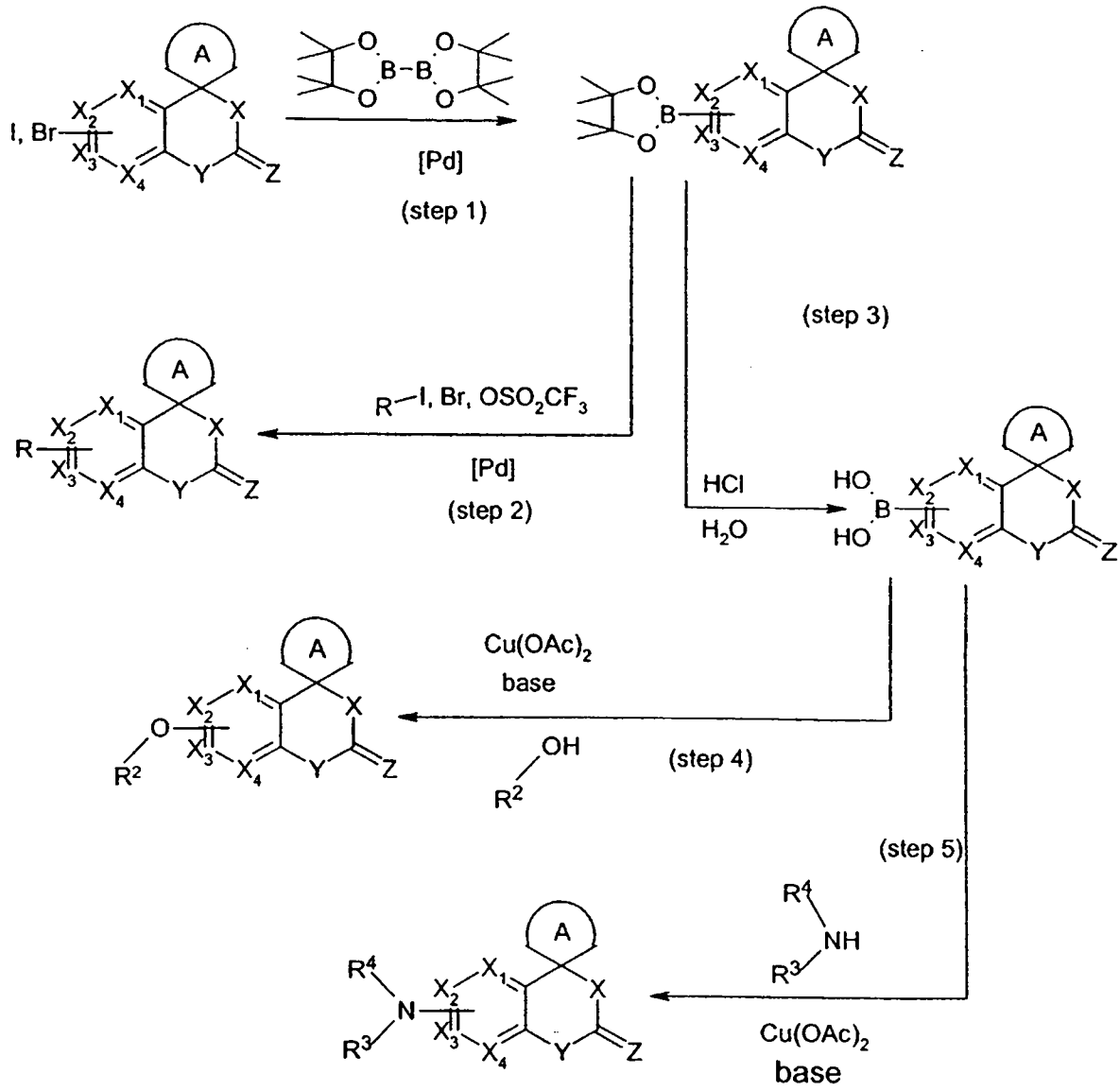
M = $B(OR')_2$, ZnHal, $SnBu_3$

In scheme 7, X_1, X_2, X_3 and X_4, X, Y, Z and A are as defined in the summary of the invention, R is alkenyl, alkynyl, aryl or heteroaryl and R' is H or alkyl.

The starting aryl or heteroaryl iodide or bromide is subjected to a palladium-catalyzed cross-coupling reaction with an organometallic species, such as a boronate ester, a boronic acid, an organozinc (Hal= halogen) or a trialkylstannane in the presence of base when needed. The organometallic species can be replaced with a terminal alkene or alkyne in the coupling reaction. When an alkyne is used, a source of copper(I), such as copper iodide, can be added. Various palladium catalysts, solvents and reaction conditions can be used for these coupling reactions and will be easily determined by the skilled person. For example, the starting aryl or heteroaryl iodide or bromide can be reacted with a boronic acid in dimethylformamide at 80°C in the presence of tetrakis(triphenylphosphine)palladium as catalyst and an aqueous solution of potassium carbonate as a base.

Protocol H:

Scheme 8



In scheme 8, X_1, X_2, X_3, X_4, X, Y, Z, R^2, R^3, R^4 and A are as defined in the summary of the invention and R is selected from aryl, alkenyl, alkynyl or heteroaryl.

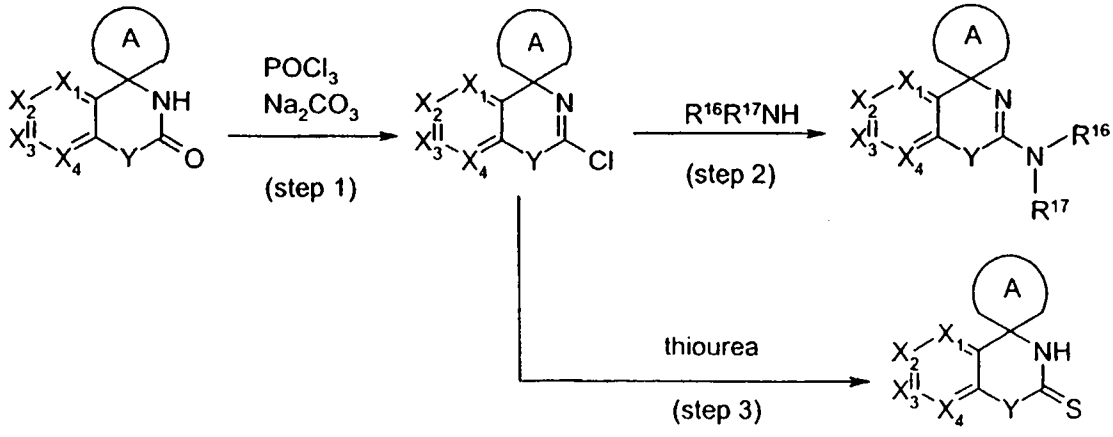
In step 1, the starting aryl or heteroaryl iodide or bromide is treated with bis(pinacolato)diboron under palladium catalysis to give the corresponding boronate ester. Various paladium catalysts, solvents and reaction conditions can be used and will be easily determined by the skilled person. For example, the starting heteroaryl iodide or bromide can be reacted with bis(pinacolato)diboron in dimethylformamide at 80°C in the presence of tetrakis(triphenylphosphine)

palladium as catalyst. The resulting boronate ester is then coupled to an aryl, alkenyl, alkynyl or heteroaryl iodide, bromide or triflate catalyzed by a palladium species (step 2). Again, various paladium catalysts, solvents and reaction conditions can be used for this coupling reactions and will be easily determined by the skilled person. For instance, the boronate ester is reacted with an aryl, alkenyl, alkynyl or heteroaryl iodide in dimethylformamide at 80°C in the presence of sodium acetate as base and tetrakis(triphenylphosphine)palladium as catalyst to give the coupled product.

In step 3, the boronate ester is hydrolyzed to the corresponding boronic acid. This can be done by treating it with acid, e.g. an aqueous solution of hydrochloric acid, in an organic solvent, e.g. methanol. The resulting boronic acid is coupled,
(step 4) under air with a phenol or heteroaryl alcohol, or,
(step 5) with a primary or secondary amine, heteroarylamine, aniline, amide, sulfonamide, urea, carbamate or imide,
in the presence of a base such as triethylamine or pyridine and a source of copper(II) such as copper(II) acetate in a solvent like dichloromethane. Molecular sieves, 4Å or 3Å, can be added to the reaction mixture.

Protocol I:

Scheme 9



In scheme 9, X_1, X_2, X_3 and X_4, Y, R^{16}, R^{17} and A are as defined in the summary of the invention.

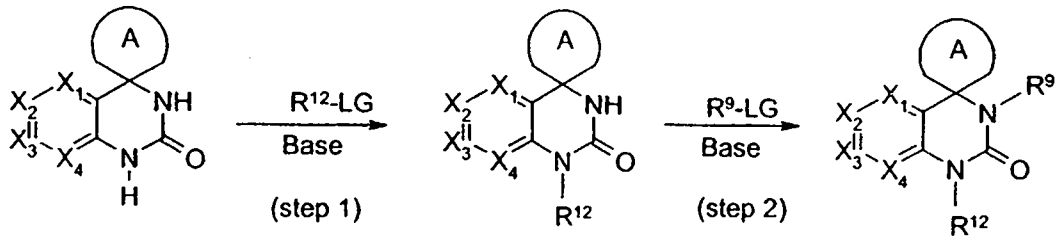
In step 1, urea, carbamate or thio carbamate is initially converted into a halo-imine via a chlorinating agent such as $POCl_3$ which is then further reacted (step 2) with a suitable amine to form the final compound. The reaction can be carried out without solvent or in a solvent, for example an alcohol such as ethanol, at a temperature between 40 and 80°C or under pressure for volatile amine, for example.

In step 3, the halo-imine is transformed into thio-derivative with thiourea.

The process of scheme 9 above can also be applied to compounds of formula (I) in which Y is NH and X is N-R^9.

Protocol J:

Scheme 10



In scheme 10, X_1, X_2, X_3, X_4, R^9, R^{12} and A are as defined in the summary of the invention and LG is a leaving group such as trifuoromethane sulfonate, mesylate or halogen.

In step 1, the quinazolinone is reacted with R^{12}-LG to obtain the N-substituted quinazoline

In step 2, the N-substituted quinazolinone is reacted with R^9-LG.

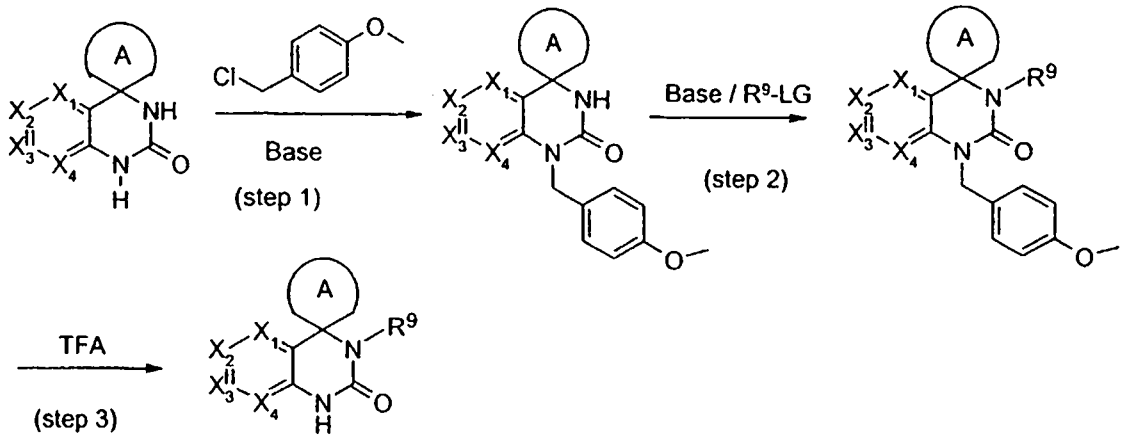
Various solvents, operating conditions and bases can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction sodium hydride or cesium carbonate as base in dimethylformamide as solvent.

Step 2 of the above process can also be applied to compounds of formula (I) in which Y is O or S.

Step 1 of the above process can also be applied to compounds of formula (I) in which X is O or S.

Protocol K:

Scheme 11



In scheme 11, X_1, X_2, X_3, X_4, R^9 and A are as defined in the summary of the invention and LG is a leaving group such as trifuoromethane sulfonate, mesylate or halogen.

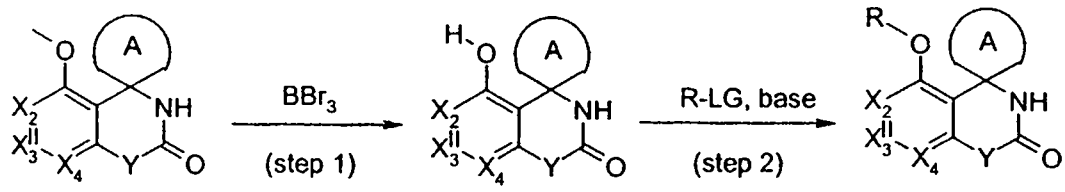
In step 1, the quinazolinone is reacted with paramethoxy-benzyl chloride (PMB). Other protecting group can be used. Various solvents, operating conditions, bases, can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction cesium carbonate as base in dimethylformamide as solvent.

In step 2, the protected quinazolinone is reacted with R^9-LG. Various solvents, operating conditions, bases, can be used and will be easily determined by the skilled person. For example, and without any limitation, one can use for the reaction sodium hydride as base in dimethylformamide as solvent.

In step 3, treatment of the N1-PMB protected quinazolinone with TFA removed the protecting group. Other protecting groups and deprotecting conditions can be used.

Protocol L:

Scheme 12



In scheme 12, X_2, X_3, X_4, and A and Y are as defined in the summary of the invention, R is alkyl or C(=O)-alkyl and LG is a leaving group.

In step 1, the starting methoxy derivative is demethylated with boron tribromide in a solvent such as dichloromethane. The resulting phenol intermediate is treated in step 2 with an electrophile such as an alkyl halide, an acyl halide or the like in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride in a solvent like dimethylformamide.

Synthesis Examples

Examples 1 to 100 illustrate, without limiting it, the synthesis of particularly active compounds of formula (I) according to the invention.

In the following experimental protocols, the proton NMR data was acquired with a 400 MHz NMR apparatus unless specifically notified.

Example 1

Spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A. Phenyl urea (13.6 g, 0.1 mol) was added portionwise to a solution of polyphosphoric acid (100 g) stirred at 100°C. After complete dissolution of the urea, cyclohexanone (10.3 mL, 0.1 mol) was added dropwise to the hot mixture. The mixture was stirred at 100-120°C until completion and poured into cold water. The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the

precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in ethanol. The title compound was obtained as a white powder. Melting point (mp) = 224-226°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.11 (br s, 1H, NH), 7.24 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.74 (br s, 1H, NH), 1.79-1.63 (m, 7H), 1.50 (m, 2H),), 1.20 (m, 1H).

Example 2

6'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-O-CH_3, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-methoxyphenyl urea (30 g, 0.18 mol) and cyclohexanone (18.6 mL, 0.18 mol) in polyphosphoric acid (200 mL). The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in ethanol. The title compound was obtained as a white powder (8.2 g, 18% yield). mp = 233-235°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.94 (br s, 1H, NH), 6.80 (br s, 1H), 6.72 (m, 2H), 6.61 (m, 1H), 3.69 (s, 3H), 1.76-1.47 (m, 9H), 1.23 (m, 1H).

Example 3

Spiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=CH, A=cycloheptyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using phenyl urea (27.2 g, 0.2 mol) and cycloheptanone (23.5 mL, 0.2 mol) in polyphosphoric acid (200 mL). The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in ethanol. The title compound was obtained as a white powder (14.7 g, 32% yield) mp = 198-200°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.11 (br s, 1H, NH), 7.21 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.88 (m, 2H), 6.78 (d, *J* = 7.9 Hz, 1H), 1.94-1.72 (m, 6H), 1.54 (m, 6H).

Example 4

7'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=C-O-CH_3, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 3-methoxyphenyl urea (33.2 g, 0.2 mol) and cyclohexanone (20.7 mL, 0.2 mol) in polyphosphoric acid (200 mL). The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in ethanol. The title compound was obtained as a white powder (9.8 g, 20% yield) mp = 228-230°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.03 (br s, 1H, NH), 7.13 (d, *J* = 8.5 Hz, 1H), 6.74 (br s, 1H, NH), 6.45 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 3.68 (s, 3H), 1.78-1.59 (m, 7H), 1.47 (m, 2H), 1.20 (m, 1H).

Example 5

6'-Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-phenyl, X_3=CH, X_4=CH, A=cycloheptyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-phenyl-phenyl urea (42.4 g, 0.2 mol) and cycloheptanone (23.5 mL, 0.2 mol) in polyphosphoric acid (400 g). The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in ethanol. The title compound was obtained as a white powder (23.3 g, 38% yield). mp = 180-182°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br s, 1H, NH), 7.59 (m, 2H), 7.43 (m, 4H), 7.30 (m, 1H), 7.0 (br s, 1H, NH), 6.88 (m, 1H), 2.01 (m, 2H), 1.89 (m, 2H), 1.77 (m, 2H), 1.58 (m, 6H).

Example 6

8'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-O-CH_3, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-methoxyphenyl urea (49.8 g, 0.3 mol) and cyclohexanone (31 mL, 0.3 mol) in polyphosphoric acid (600 g). The precipitate was filtered, washed with cold water, taken up in hot ethanol and neutralized with NH_4OH solution. Water was added to make a 50% ethanol/water solution and the precipitate was filtered, washed with water and dried. The crude material was purified by crystallization in isopropanol. The title compound was obtained as a white powder (48.1 g, 65% yield). mp = 209-211°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.79 (br s, 1H, NH), 6.87 (m, 4H), 3.79 (s, 3H), 1.79-1.60 (m, 7H), 1.48 (m, 2H), 1.22 (m, 1H).

Example 7

8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-chlorophenyl urea (51.15 g, 0.3 mol) and cyclohexanone (29.4 g, 0.3 mol) in polyphosphoric acid (600 g). The precipitate was filtered, washed with cold water and recrystallized from ethyl acetate. The title compound was obtained as an orange solid (21% yield). mp = 209-211°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.42 (br s, 1H, NH), 7.29 (d, J = 7.9 Hz, 2H), 7.16 (br s, 1H, NH), 6.95 (t, J = 7.9 Hz, 1H), 1.81 - 1.61 (m, 7H), 1.52-1.39 (m, 2H), 1.25-1.22 (m, 1H).

Example 8 and Example 9

7'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (Example 8)

X_1=CH, X_2=CH, X_3=C-Cl, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

and 5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (Example 9)

X_1=C-Cl, X_2=CH, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compounds were prepared according to protocol A, using 3-chlorophenyl urea (0.51 g, 3 mmol) and cyclohexanone (0.5 mL, 4.8 mmol, 1.6 equiv.) in polyphosphoric acid (11 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3CN : 90/10 to 60/40) followed by recrystallization in toluene to give 7'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid (110 mg, 15% yield). mp = 254°C. ^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br s, 1H, NH), 7.27 (d, J = 8.0 Hz, 1H), 6.91-6.89 (m, 2H), 6.82 (s, 1H, NH), 1.83-1.61 (m, 7H), 1.49 (m, 2H), 1.24 (m, 1H).

and 5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid (101 mg, 14% yield). mp = 229°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.34 (br s, 1H, NH), 7.11 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.84 (br s, 1H, NH), 6.77 (d, J = 8.0 Hz, 1H), 2.60 (td, J = 13.0, 4.0 Hz, 2H), 1.82 (m, 2H), 1.64-1.49 (m, 5H), 1.22 (m, 1H).

Example 10

8'-Methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-CH_3, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using o-tolyl urea (551 mg, 3.66 mmol) and cyclohexanone (430 µL, 4.15 mmol, 1.1 equiv.) in polyphosphoric acid (5 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by

recrystallization in toluene to give 290 mg (34% yield) of the title compound as a white solid. mp = 204°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.32 (br s, 1H, NH), 7.10 (d, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 7.10 (m, 2H), 1.82 - 1.61 (m, 7H), 1.50 (m, 2H), 1.23 (m, 1H).

Example 11

6'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-Cl, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-chlorophenyl urea (0.85 g, 5 mmol) and cyclohexanone (0.55 mL, 5.5 mmol, 1.1 equiv.) in polyphosphoric acid (29 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 79 mg (6% yield) of the title compound as a white solid. mp = 241°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.28 (br s, 1H, NH), 7.29 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.87 (br s, 1H, NH), 6.81 (d, *J* = 8.5 Hz, 1H), 1.76 - 1.60 (m, 7H), 1.49 (m, 2H), 1.25 (m, 1H).

Example 12

8'-Bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-bromophenyl urea (1.075 g, 5 mmol) and cyclohexanone (0.6 mL, 5.8 mmol, 1.2 equiv.) in polyphosphoric acid (39 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 415 mg (28% yield) of the title compound as a white solid. mp = 213°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.86 (br s, 1H, NH), 7.45 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.17 (br s, 1H, NH), 6.90 (t, *J* = 8.0 Hz, 1H), 1.81-1.49 (m, 9H), 1.23 (m, 1H).

Example 13

8'-Fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-F, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-fluorophenyl urea (0.77 g, 5 mmol) and cyclohexanone (0.55 mL, 5.5 mmol, 1.1 equiv.) in polyphosphoric acid (20 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 95/5) followed by recrystallization in toluene to give 272 mg (23% yield) of the title compound as a white solid. mp = 221°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.12 (br s, 1H, NH), 7.11 (d, *J* = 7.8 Hz, 1H), 7.05 (m, 1H), 6.94(br s, 1H, NH), 6.90 (m, 1H), 1.81-1.61 (m, 7H), 1.50 (m, 2H), 1.25 (m, 1H).

Example 14

6'-Methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-CH_3, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-methylphenyl urea (1.5 g, 10 mmol) and cyclohexanone (1.1 mL, 11 mmol, 1.1 equiv.) in polyphosphoric acid (38 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 405 mg (18% yield) of the title compound as a white solid. mp = 229°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.01 (br s, 1H, NH), 7.05 (s, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.68-6.66 (m, 2H), 2.22 (s, 3H), 1.76 - 1.61 (m, 7H), 1.50 (m, 2H), 1.23 (m, 1H).

Example 15

5',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=C-Cl, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2,5-dichlorophenyl urea (0.615 g, 3 mmol) and cyclohexanone (0.50 mL, 5 mmol, 1.6 equiv.) in polyphosphoric acid (15 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 92/8) followed by recrystallization in toluene to give 56 mg (7% yield) of the title compound as a white solid. mp = 243°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.35 (br s, 1H, NH), 7.35 (d, *J* = 8.5 Hz, 1H), 7.21 (br s, 1H, NH), 7.01 (d, *J* = 9.0 Hz, 1H), 2.50 (ddd, *J* = 13.5, 13.5, 4.5 Hz, 2H), 1.83 (m, 2H), 1.68-1.51 (m, 5H), 1.24 (m, 1H).

Example 16 and Example 17

6',7'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (Example 16)

X_1=CH, X_2=C-Cl, X_3=C-Cl, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

and 5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (Example 17)

X_1=C-Cl, X_2=C-Cl, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compounds were prepared according to protocol A, using 3,4-dichlorophenyl urea (0.61 g, 3 mmol) and cyclohexanone (0.50 mL, 5 mmol, 1.6 equiv.) in polyphosphoric acid (16 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3CN : 90/10 to 60/40) followed by recrystallization in toluene to give 6',7'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid (55 mg, 6% yield). mp = 269°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.40 (br s, 1H, NH), 7.51 (s, 1H), 7.03 (br s, 1H, NH), 6.98 (s, 1H), 1.75 - 1.59 (m, 7H), 1.48 (m, 2H), 1.24 (m, 1H).

and 5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid (26 mg, 3% yield). mp = 240°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.47 (br s, 1H, NH), 7.43 (d, J = 8.5 Hz, 1H), 6.91 (br s, 1H, NH), 6.81 (d, J = 9.0 Hz, 1H), 2.64 (ddd, J = 13.4, 13.4, 4.4 Hz, 2H), 1.83 (m, 2H), 1.65-1.53 (m, 5H), 1.26 (m, 1H).

Example 18

6'-Phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-phenyl, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-phenyl-phenyl urea (0.67 g, 3.15 mmol) and cyclohexanone (0.50 mL, 5 mmol, 1.6 equiv.) in polyphosphoric acid (16 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 410 mg (13% yield) of the title compound as a white solid. mp = 213°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.25 (br s, 1H, NH), 7.62 (d, J = 7.4 Hz, 2H), 7.52 (d, J = 1.6 Hz, 1H), 7.42 (m, 3H), 7.30 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.83 (br s, 1H, NH), 1.84 - 1.79 (m, 6H), 1.63 (m, 1H), 1.53 (m, 2H), 1.30 (m, 1H).

Example 19

8'-Iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-I, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-iodophenyl urea (2 g, 7.6 mmol) and cyclohexanone (1 mL, 9.6 mmol, 1.25 equiv.) in polyphosphoric acid (25 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 80mg (3% yield) of the title compound as a white solid. mp = 256°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.26 (br s, 1H, NH), 7.52 (m, 1H), 7.44 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.87 (br s, 1H, NH), 6.62 (d, *J* = 8.3 Hz, 1H), 1.78 - 1.62 (m, 7H), 1.54 (m, 2H), 1.26 (m, 1H).

Example 20

8'-Bromospiro[cyclobutane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=cyclobutyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-bromophenyl urea (0.6 g, 2.8 mmol) and cyclobutanone (0.25 mL, 3.35 mmol, 1.2 equiv.) in polyphosphoric acid (22 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH :99/1 to 90/10) and the resulting powder was washed with diisopropyl ether. The title compound was obtained as a white powder (0.03 g, 4% yield). mp = 203-205°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (br s, 1H, NH), 7.80 (br s, 1H, NH), 7.50 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 2.46-2.39 (m, 4H), 1.86 (m, 2H).

Example 21

8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=cycloheptyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-bromophenyl urea (0.6 g, 2.8 mmol) and cycloheptanone (0.5 mL, 4.2 mmol, 1.5 equiv.) in polyphosphoric acid (22 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The organic extracts are dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH :99/1 to 90/10) and the resulting powder was washed with

diisopropyl ether. The title compound was obtained as a white powder (0.12 g, 14% yield).mp = 215-217°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.87 (br s, 1H, NH), 7.44 (d, *J* = 7.8 Hz, 1H), 7.31 (br s, 1H, NH), 7.28 (d, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 1.96-1.84 (m, 4H), 1.76-1.71 (m, 2H), 1.56 (m, 6H).

Example 22

8'-Bromo-4-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=4-methyl-cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-bromophenyl urea (0.6 g, 2.8 mmol) and 4-methylcyclohexanone (0.41 mL, 3.35 mmol, 1.2 equiv.) in polyphosphoric acid (22 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH :99/1 to 90/10) and the resulting powder was washed with diisopropyl ether. The title compound was obtained as a white powder (0.11 g, 11% yield). mp = 187-189°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.85 (br s, 1H, NH), 7.44 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.14 (br s, 1H, NH), 6.89 (t, *J* = 7.8 Hz, 1H), 1.75 (m, 4H), 1.56-1.43 (m, 5H),), 1.85 (d, *J* = 6.2 Hz, 3H).

Example 23

8'-Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A= bicyclo[3,2,1]octane, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2-bromophenyl urea (0.6 g, 2.8 mmol) and bicyclo[3.2.1]octan-2-one (0.55 g, 4.47 mmol, 1.6 equiv.) in polyphosphoric acid (22 g). The aqueous layer was extracted with CH_2Cl_2/MeOH (2/1). The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica

gel (CH_2Cl_2/MeOH :99/1 to 90/10) and the resulting powder was washed with diisopropyl ether. The title compound was obtained as a white powder (0.003 g, 1% yield). mp = 276-278°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.92 (br s, 1H, NH), 7.48 (d, *J* = 7.7 Hz, 1H), 7.42 (br s, 1H, NH), 7.39 (d, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 2.33 (td, *J* = 13.8, 5.7 Hz , 1H), 2.15-2.10 (m, 3H), 1.98 (d, *J* = 11.5 Hz, 1H), 1.58-1.52 (m, 2H), 1.37-1.28 (m, 4H), 1.18 (m, 1H).

Example 24

6',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-Cl, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of Example 7 (100.2 mg, 0.4 mmol) in dimethylformamide (2 mL) was treated with N-chlorosuccinimide (80 mg, 0.6 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 100/0 to 90/10) and reverse phase HPLC (C18 column, gradient of acetonitrile in water : 50/50 to 95:5) to give the title compound as a white solid (48% yield). mp = 245°C

^{1}H NMR [$CDCl_3$] δ 7.26 (m, 1H), 7.19 (br s, 1H, NH), 7.10 (m, 1H), 5.80 (br s, 1H, NH), 1.97 (m, 2H), 1.82-1.57 (m, 7H), 1.29 (m, 1H).

Example 25

8'-Chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-I, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a solution of Example 7 (5 g, 20 mmol) in trifluoroacetic acid (25 mL) were subsequently added N-iodosuccinimide (6 g, 22 mmol, 1.1 equiv.) and sulfuric acid (4 mL). The resulting solution was heated to 55°C overnight, concentrated under reduced pressure, taken into dichloromethane and washed twice with water. The reaction mixture was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 97/3) to give 4.5 g (73% yield) of the title compound as a yellowish solid. mp = 261°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (br s, 1H, NH), 7.64 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 1.0 Hz, 1H), 7.22 (br s, 1H, NH), 1.76 - 1.59 (m, 7H), 1.49 (m, 2H), 1.25 (m, 1H).

Example 26

8'-Chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-phenyl, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of Example 18 (232 mg, 0.79 mmol) in dimethylformamide (4 mL) was treated with N-chlorosuccinimide (80 mg, 0.6 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) to give the title compound as a white solid (41% yield). mp = 226°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (br s, 1H, NH), 7.68 (d, *J* = 7.3 Hz, 2H), 7.60 (s, 1H), 7.56 (s, 1H), 7.44 (t, *J* = 7.1 Hz, 2H), 7.34 (m, 1H), 7.15 (br s, 1H, NH), 1.88-1.22 (m, 10H).

Example 27

8'-Chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-O-CH_3, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of Example 2 (500 mg, 2.03 mmol) in dimethylformamide (10 mL) was treated with N-chlorosuccinimide (300 mg, 2.24 mmol, 1.1 equiv.) at 60°C overnight. The reaction mixture was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 76 mg (13% yield) of the title compound as a white solid. mp = 226°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.20 (br s, 1H, NH), 6.96 (br s, 1H, NH), 6.92 (m, 1H), 6.87 (m, 1H), 3.73 (s, 3H), 1.72 - 1.61 (m, 7H), 1.62 (m, 2H), 1.26 (m, 1H).

Example 28

8'-Chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-

2'(1'H)-one

X_1=CH, X_2=C-phenyl, X_3=CH, X_4=C-Cl, A=cycloheptyl, X=NH, Z=O, Y=NH

A solution of Example 5 (150 mg, 0.49 mmol) in dimethylformamide (2 mL) was treated with N-chlorosuccinimide (75 mg, 0.56 mmol, 1.1 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10) to give 158 mg (95% yield) of the title compound as a yellowish solid. mp = 201°C

^{1}H NMR [($CDCl_3$] δ 7.51-7.41 (m, 6H), 7.36 (m, 2H), 5.90 (br s, 1H, NH), 2.75-2.01 (m, 4H), 1.77-1.43 (m, 8H).

Example 29

8'-Chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-CH_3, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of Example 14 (350 mg, 1.51 mmol) in dimethylformamide (7 mL) was treated with N-chlorosuccinimide (305 mg, 2.3 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 90/10). The resulting solid was triturated with methanol to give the title compound as a white solid (28% yield). mp = 266°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.23 (br s, 1H, NH), 7.11 (m, 2H), 7.03 (br s, 1H, NH), 2.23 (s, 3H), 1.77 - 1.61 (m, 7H), 1.51 (m, 2H), 1.25 (m, 1H).

Example 30

8'-Chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(3-pyridyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (0.5 g, 1.4 mmol) in dimethylformamide (5 mL) were subsequently added 3-pyridylboronic acid (0.22 g, 1.7 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL). The mixture was

degassed by bubbling nitrogen for 30 minutes and tetrakistriphenylphosphine palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, triturated with water and filtered. The resulting solid was triturated with ethyl acetate, filtered and purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc : 80/20 to 50/50) to give 140 mg (30% yield) of the title compound as white solid. mp = 246°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.93 (br s, 1H, NH), 8.55 (m, 2H), 8.10 (m, 1H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.45 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.19 (br s, 1H, NH), 1.91 - 1.77 (m, 6H), 1.63 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 31

8'-Chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(4-pyridyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (0.5 g, 1.4 mmol) in dimethylformamide (5 mL) were subsequently added 4-pyridylboronic acid (0.22 g, 1.7 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakistriphenylphosphine palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, washed with water and ethyl acetate then purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc : 80/20 to CH_2Cl_2/MeOH : 97/3) to give 40 mg (10% yield) of the title compound as white solid. mp = 320-321°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (br s, 1H, NH), 8.59 (d, *J* = 6.0 Hz, 2H), 7.80-7.72 (m, 4H), 7.22 (br s, 1H, NH), 1.99 - 1.77 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 32

6'-(4-Carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(4-carboxyphenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (1 g, 2.8 mmol) in dimethylformamide (10 mL) were subsequently added 4-carboxyphenylboronic acid (0.55 g, 3.35 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (3 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakistriphenylphosphine palladium (120 mg, 0.1 mmol, 0.04 equiv.) was added. After heating to 90°C for 4 hours, the mixture was concentrated under reduced pressure, taken into ethyl acetate and washed with water. The aqueous layer was acidified to pH 2 and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to a third of its volume and filtered. The resulting solid was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 97/3 to 95/5) to give 250 mg (40% yield) of the title compound as white solid. mp = 309°C

^{1}H NMR [$(CD_3)_2SO$] δ 12.95 (br s, 1H, OH), 8.58 (br s, 1H, NH), 7.98 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.65 (s, 1H), 7.20 (br s, 1H, NH), 1.93 - 1.78 (m, 6H), 1.64 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 33

6'-(3-Carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(3-carboxyphenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (1 g, 2.8 mmol) in dimethylformamide (10 mL) were subsequently added 3-carboxyphenylboronic acid (0.55 g, 3.35 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (3 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakistriphenylphosphine palladium (120 mg, 0.1 mmol, 0.04 equiv.) was added. After heating to reflux overnight, the mixture was concentrated under reduced pressure, taken into dichloromethane and washed with water. The aqueous layer was acidified to pH 1 and filtered to give 330 mg (58% yield) of the title compound as white solid. mp = 300°C

^{1}H NMR [$(CD_3)_2SO$] δ 13.10 (br s, 1H, OH), 8.54 (br s, 1H, NH), 8.14 (s, 1H), 7.92 (t, *J* = 7.5 Hz, 2H), 7.64 (d, *J* = 1.5 Hz, 1H), 7.59-7.55 (m, 2H), 7.17 (br s, 1H, NH), 1.89 - 1.78 (m, 6H), 1.64 (m, 1H), 1.55 (m, 2H), 1.32 (m, 1H).

Example 34

8'-Chloro-6'-(1*H*-indol-5-yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-indol-5-yl, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (0.5 g, 1.4 mmol) in dimethylformamide (5 mL) were subsequently added 5-indolylboronic acid (0.26 g, 1.6 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakistriphenylphosphine palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 80°C overnight, the mixture was concentrated under reduced pressure, taken into ethyl acetate and washed three times with water. The residue was then purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc : 80/20) to give 210 mg (44% yield) of the title compound as white solid. mp = 257°C

^{1}H NMR [$(CD_3)_2SO$] δ 11.12 (br s, 1H, NH), 8.40 (br s, 1H, NH), 7.83 (s, 1H), 7.56 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.11 (s, 1H), 6.47 (br s, 1H, NH), 1.89 - 1.78 (m, 6H), 1.64 (m, 1H), 1.55 (m, 2H), 1.32 (m, 1H).

Example 35

8'-Chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(2-pyridyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a solution of Example 25 (0.5 g, 1.3 mmol) in tetrahydrofuran (5 mL) was added a 0.5 M solution of 2-pyridyl zinc bromide in tetrahydrofuran (60 µL, 30 mmol, 23 equiv.). The mixture was degassed bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine)palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After refluxing for 4 h, additional tetrakis(triphenylphosphine)palladium (100 mg) and toluene (5 mL) were added. After heating to 90°C overnight, the

mixture was diluted with dichloromethane and washed three times with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc : 90/10) to give 50 mg (2% yield) of the title compound as a solid. mp = 251°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.64 (br s, 1H, NH), 7.45 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.04-8.01 (m, 3H), 7.85 (td, *J* = 7.5, 2.0 Hz, 1H), 7.32 (m, 1H), 7.21 (br s, 1H, NH), 1.89 - 1.83 (m, 6H), 1.66 (m, 1H), 1.56 (m, 2H), 1.32 (m, 1H).

Example 36

8'-Chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(3-dimethylaminoprop-1-ynyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 25 (0.5 g, 1.4 mmol) in pyrrolidine (10 mL) were subsequently added 1-dimethylamino-2-propyne (0.170 mL, 1.6 mmol, 1.2 equiv.), toluene (10 mL) and tetrakis(triphenylphosphine) palladium (80 mg, 0.07 mmol, 0.05 equiv.). After heating to 45°C overnight, the mixture was filtered, diluted with ethyl acetate and washed twice with a 1 M aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate, concentrated under reduced pressure and to give 60 mg (13% yield) of the title compound as yellowish solid. mp = 208°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.63 (br s, 1H, NH), 7.37 (d, *J* = 1.5 Hz, 1H), 7.34 (s, 1H), 7.19 (br s, 1H, NH), 3.43 (s, 2H), 2.24 (s, 6H), 1.81 - 1.72 (m, 6H), 1.62 (m, 1H), 1.50 (m, 2H), 1.27 (m, 1H).

Example 37

8'-Chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(3-methylaminoprop-1-ynyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a solution of Example 25 (0.2 g, 0.5 mmol)) in dimethylformamide (3mL) were subsequently added N-methylpropargylamine (0.1 mL, 1 mmol, 2 equiv.) and triethylamine (1 mL, 7 mmol, 14 equiv.). The mixture was degassed bubbling nitrogen for 30 minutes then tetrakis(triphenylphosphine)palladium (20 mg, 0.025 mmol, 0.05 equiv.) and copper(I) iodide (20 mg, 0.1 mmol, 0.02 equiv.) were added. After heating to 80°C overnight, the mixture was diluted with dichloromethane and washed three times with water. The organic layer was dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 98/2 to CH_2Cl_2/MeOH/NH_4OH : 96/3/1) to give 40 mg (25% yield) of the title compound as a solid. mp = 188°C

^1H NMR [$(CD_3)_2SO$] δ 8.62 (br s, 1H, NH), 7.33 (s, 1H), 7.32 (s, 1H), 7.19 (br s, 1H, NH), 3.50 (br s, 2H), 2.35 (br s, 3H), 1.76 - 1.73 (m, 6H), 1.61 (m, 1H), 1.50 (m, 2H), 1.26 (m, 1H).

Example 38

8'-Chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-(4-(4-methyl-piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (100 mg, 0.27 mmol) in toluene (3 mL) was added thionyl chloride (0.03 mL, 0.4 mmol, 1.5 equiv.). The resulting mixture was heated to reflux for 2 hours, then twice concentrated under reduced pressure and taken into toluene. To the resulting solid in toluene (2 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 1-methylpiperazine (0.04 mL, 0.32 mmol, 1.2 equiv.). After stirring overnight, the mixture was diluted with dichloromethane and washed twice with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 97/3) to give 20 mg (16% yield) of the title compound as white solid. mp = 277°C

1H NMR [$(CD3)_2SO$] δ 8.55 (br s, 1H, NH), 7.80 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.18 (br s, 1H, NH), 3.60 (br m, 4H), 3.08

(br m, 4H), 2.67 (br s, 3H), 1.91 - 1.72 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 39

8'-Chloro-6'-[4-(3-*N*-dimethylamino-propylcarboxamide)phenyl]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-[4-(3-*N*-dimethylamino-propylcarboxamide)phenyl], X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (122 mg, 0.33 mmol) in toluene (3 mL) was added thionyl chloride (0.04 mL, 0.5 mmol, 1.5 equiv.). The resulting mixture was heated to reflux overnight, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.1 mL, 0.54 mmol, 1.6 equiv.) and 3-dimethylaminopropylamine (0.037 mL, 0.26 mmol, 0.8 equiv.). After stirring for 4 h, the mixture was diluted with dichloromethane and washed twice with water and a 1N aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 40 mg (34% yield) of the title compound as white solid. mp = 232°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.59-8.55 (m, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.63 (s, 1H), 7.18 (br s, 1H, NH), 3.29 (m, 2H), 2.26 (t, *J* = 7.0 Hz, 2H), 2.14 (s, 6H), 1.92 - 1.77 (m, 6H), 1.67 (m, 3H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 40

8'-Chloro-6'-[4-(2-*N*-dimethylamino-ethylcarboxamide)phenyl]spiro-[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-[4-(2-*N*-dimethylamino-ethylcarboxamide)phenyl], X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (150 mg, 0.4 mmol) in toluene (3 mL) was added thionyl chloride (0.03 mL, 0.41 mmol, 1.0 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the

resulting solid in toluene (3 mL) was added triethylamine (0.14 mL, 0.8 mmol, 2 equiv.) and 2-dimethylaminoethylamine (0.04 mL, 0.32 mmol, 0.8 equiv.). After stirring overnight, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1N aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 100 mg (56% yield) of the title compound as white solid. mp = 234°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.54 (br s, 1H, NH), 8.44 (t, *J* = 5.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.63 (d, *J* = 1.5 Hz, 1H), 7.18 (br s, 1H, NH), 3.37 (q, *J* = 6.5 Hz, 2H), 2.45 (t, *J* = 6.5 Hz, 2H), 2.22 (s, 6H), 1.90 - 1.74 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 41

8'-Chloro-6'-[3-(3-*N*-dimethylamino-propylcarboxamide)phenyl]spiro[-cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-[3-(3-*N*-dimethylamino-propylcarboxamide)phenyl], X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 33 (100 mg, 0.27 mmol) in toluene (10 mL) was added thionyl chloride (0.1 mL, 1.3 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (10 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 3-dimethylaminopropylamine (0.03 mL, 0.21 mmol, 0.8 equiv.). After stirring for 3 h, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 30 mg (30% yield) of the title compound as white solid. mp = 208°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.60 (m, 1H), 8.54 (br s, 1H, NH), 8.03 (br s, 1H, NH), 7.83 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.60 (s, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.17 (br s, 1H, NH), 3.29 (m, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 2.14 (s, 6H), 1.85 - 1.78 (m, 6H), 1.67 (m, 3H), 1.55 (m, 2H), 1.30 (m, 1H).

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Example 42

8'-Chloro-6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-[3-(4-methyl-piperazine-1-carbonyl)-phenyl], X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 33 (100 mg, 0.27 mmol) in toluene (5 mL) was added thionyl chloride (0.03 mL, 0.4 mmol, 1.5 equiv.). The resulting mixture was heated to reflux for 3 hours, then twice concentrated under reduced pressure and taken into toluene. To the resulting solid in toluene (5 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 1-methylpiperazine (0.024 mL, 0.21 mmol, 0.8 equiv.). After stirring overnight, the mixture was diluted with dichloromethane and washed twice with water. The organic layer was concentrated under reduced pressure, taken into ethyl acetate and washed with a 1N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 60 mg (61% yield) of the title compound as white solid. mp = 207°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.52 (br s, 1H, NH), 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 7.58 (d, *J* = 1.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.16 (br s, 1H, NH), 3.64 (br m, 4H), 2.32 (br m, 4H), 2.20 (s, 3H), 1.89 - 1.77 (m, 6H), 1.64 (m, 1H), 1.53 (m, 2H), 1.32 (m, 1H).

Example 43

8'-Chloro-6'-[3-(2-*N*-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=CH, X_2=C-[3-(2-*N*-dimethylamino-ethylcarboxamide)phenyl], X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 33 (100 mg, 0.27 mmol) in toluene (10 mL) was added thionyl chloride (0.1 mL, 1.3 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the

resulting solid in toluene (10 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 2-dimethylaminoethyl amine (0.024 mL, 0.21 mmol, 0.8 equiv.). After stirring for 3 h, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 40 mg (40% yield) of the title compound as white solid. mp = 225°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (br s, 1H, NH), 8.51 (t, *J* = 5.5 Hz, 1H), 8.05 (br s, 1H, NH), 7.84 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.18 (br s, 1H, NH), 3.39 (q, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 2.19 (s, 6H), 1.89 - 1.78 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 44

8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-thione

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=S, Y=NH

a) Preparation of 2',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (intermediate 1)

A solution of Example 7 (51 mg, 2 mmol) in phosphorus oxychloride (10 mL) containing Na_2CO_3 (32 mg, 3 mmol) was heated at 95°C for 5 hours. After cooling to room temperature, the phosphorus oxychloride was removed under reduced pressure. The crude product was used without purification in the next step.

^{1}H NMR [$(CD_3)_2SO$] δ 8.31 (br s, 1H, NH), 7.28 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 1.89-1.61 (m, 7H), 1.51-1.48 (m, 2H), 1.28-1.24 (m, 1H).

b) Preparation of Example 44

A solution of 2',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (2 mmol) and thiourea (88 mg, 10.4 mmol) was heated to reflux overnight, cooled to room temperature and concentrated. The material was dissolved in EtOAc and washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous

NaCl. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc :95/5) to afford the title compound as a white solid (288 mg, 54%). mp= 209-211°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.15 (br s, 1H, NH), 8.69 (br s, 1H, NH), 7.39 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 1.85 - 1.51 (m, 9H), 1.26 (m, 1H).

Example 45

8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z^1=NH-CN, Y=N

2',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (2 mmol) and cyanamide (3 g) were heated to 60°C overnight. The mixture was cooled to room temperature and water was added. The aqueous solution was extracted with CH_2Cl_2. The organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc : 90/10) to afford the title compound as a white solid (260 mg, 23%). mp = 193-195°C

^{1}H NMR [$(CD_3)_2SO$] δ 9.45 (br s, 1H, NH), 8.05 (br s, 1H, NH), 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 1.81-1.57 (m, 9H), 1.28 (m, 1H).

Example 46

8'-Chloro-2'-methoxyiminospiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazoline]

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z^1= N-O-CH_3, Y= NH

A solution of 2',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (2 mmol) in EtOH (10 mL) was added to a solution of methoxylamine hydrochloride (1 mg, 11.9 mmol) and triethylamine (1.67 mL, 11.9 mmol) in EtOH (3 mL) and heated to reflux overnight, cooled to room temperature and concentrated. The material was dissolved in EtOAc and washed sequentially with saturated aqueous

$NaHCO_3$ and saturated aqueous NaCl. The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc :80/20 to cyclohexane/EtOAc/MeOH : 80/20/1) to afford the title compound as a white solid (120 mg, 22%). mp = 113-115°C

^1H NMR [$(CD_3)_2SO$] δ 8.17 (br s, 0.4H, NH), 7.64 (br s, 0.6H, NH), 7.33 (d, *J* = 8.0 Hz, 0.6H), 7.27 (d, *J* = 8.0 Hz, 0.6H), 7.25 (d, *J* = 7.5 Hz, 0.4H), 7.22 (d, *J* = 7.5 Hz, 0.4 H), 6.94 (t, *J* = 8.0 Hz, 0.6H), 6.87 (t, *J* = 7.5 Hz, 0.4H), 6.17 (br s, 0.6H, NH), 5.77 (br s, 0.4H, NH), 1.70 (m, 7H), 1.48 (m, 2H), 1.28 (m, 1H).

Example 47

8'-Chloro-2'-dimethylaminospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazoline]

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z^1= $N(CH_3)_2$, Y= N

A solution of 2',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (2 mmol) and dimethylamine (2M in ethanol) (3mL, 6mmol) was heated to 140°C in a sealed tube overnight, cooled to room temperature and concentrated. The material was dissolved in CH_2Cl_2 and washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic extracts were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc/NH_3 (28% in water) :70/30/1) to afford the title compound as a white solid (95 mg, 17%). mp = 173-175°C.

^1H NMR [$(CD_3)_2SO$] δ 7.14 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.73 (t, *J* = 7.8 Hz, 1H), 5.84 (br s, 1H, NH), 3.0 (s, 6H), 1.73-1.53-(m, 9H), 1.29-1.17 (m, 1H).

Example 48

8'-Chloro-1'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= N-CH_3

To a stirred solution Example 7 (150 mg, 0.59 mmol) in dimethylformamide (10 mL) was added sodium hydride (50% in grease, 35.4 mg, 0.73 mmol) under N_2. The mixture was stirred until hydrogen evolution ceased and methyl iodide (40 µl, 0.65 mmol) was added. The mixture was stirred overnight at room temperature. After removal of the solvent, the material was dissolved in CH_2Cl_2, washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc 90/10) to afford the title compound as a white solid (55 mg, 43%). mp = 163-165°C

^{1}H NMR [$(CD_3)_2SO$] δ 7.34 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.94 (br s, 1H, NH), 3.37 (s, 3H), 1.80-1.62 (m, 7H), 1.53 (m, 2H), 1.19 (m, 1H).

Example 49

8'-Chloro-1'-(ethoxycarbonylmethyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazolin]-2'(1'H)-one

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= N-(ethoxycarbonylmethyl)

To a stirred Example 7 (500 mg, 2 mmol) in dimethylformamide (10 mL) was added sodium hydride (50% in grease, 96 mg, 2 mmol) under N_2. The mixture was stirred until hydrogen evolution ceased and ethyl bromoacetate (0.77 mL, 7 mmol) was added. The mixture was stirred overnight at 80°C. After removal of the solvent under reduced pressure, the material was dissolved in CH_2Cl_2, washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc/toluene : 70/30/100) to afford the title compound as a white solid (50 mg, 7%). mp = 140-142°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.35 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.23 (br s, 1H, NH), 7.07 (t, J = 8.0 Hz, 1H), 4.71 (s, 2H), 4.09 (q, J = 7.5 Hz, 2H), 1.95-1.92 (m, 2H), 1.78-1.62 (m, 5H), 1.54-1.51 (m, 2H), 1.23 (m, 1H), 1.15 (t, J = 7.5 Hz, 3H).

Example 50

8'-Chloro-3'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= cyclohexyl, X= N-CH_3, Z= O, Y= NH

Preparation of 8'-Chloro-1'-(4-methoxybenzyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 2)

A solution of Example 7 (5 g, 19.9 mmol), cesium carbonate (7.8 g, 23.9 mmol) and 4-methoxybenzylchloride (2.9 mL, 21.93mmol) in dimethylformamide (250 mL) was stirred at room temperature for 3 days. The mixture was concentrated. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. AcOEt was added and the precipitate was filtered off to afford the title compound as a white solid (6.33 g, 86%).

^{1}H NMR [$(CD_3)_2SO$] δ 7.33 (d, *J* = 7.8 Hz , 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.06 (m, 3H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.25 (s, 2H), 3.66 (s, 3H), 1.67-1.47 (m, 5H), 1.40-1.27 (m, 4H), 1.13 (m, 1H).

Preparation of 8'-Chloro-3'-methyl-1'-(4-methoxybenzyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 3)

To a stirred solution of 8'-chloro-1'-(4-methoxybenzyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (260 mg, 0.7 mmol) in dimethylformamide (15 mL) was added sodium hydride (50% in grease, 48 mg, 1 mmol) under N_2. The mixture was stirred until hydrogen evolution ceased and methyl iodide (60 µl, 0.96 mmol) was added. The mixture was stirred overnight at room temperature. After removal of the solvent, the material was dissolved in CH_2Cl_2, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc/28% aqueous NH_3 :90/10/1) to afford the title compound as a white solid (190 mg, 70%).

^{1}H NMR [$(CD_3)_2SO$] δ 7.45 (d, *J* = 7.9 Hz , 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 5.25 (s, 2H), 3.67 (s, 3H), 2.85 (s, 3H), 1.66-1.35 (m, 10H).

Preparation of example 50

To a solution of 8'-Chloro-3'-methyl-1'-(4-methoxybenzyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (180 mg, 047 mmol) in CH_2Cl_2 (4 mL) cooled at –10°C was added dropwise trifluoroacetic acid (4 mL). The mixture was stirred at –10°C for 1 hour and at room temperature for 20 min. The mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were washed with saturated aqueous NaCl solution, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc/NH_3 (28% in water) :90/10/1 to 70/30/1) to afford the title compound as a white solid (21 mg, 17%). mp = 135-137°

^{1}H NMR [$(CD_3)_2SO$] δ 8.80 (br s, 1H, NH), 7.46 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 2.96 (s, 3H), 1.96 (m, 4H), 1.66 (m, 2H), 1.56-1.39 (m, 4H).

Example 51

8'-Chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[-cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= C-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl], X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

To a suspension of Example 32 (185 mg, 0.5 mmol) in toluene (10 mL) was added thionyl chloride (0.19 mL, 1.9 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (4 mL) was added triethylamine (0.15 mL, 1 mmol, 2 equiv.) and 2-(1-piperazinyl)pyrimidine (100 mg, 0.6 mmol, 1.2 equiv.). After heating to 80°C for 1 h, the mixture was diluted with dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the resulting solid was purified by flash chromatography on silica gel

(CH_2Cl_2/MeOH : 97/3) to give 210 mg (81% yield) of the title compound as white solid. mp = 271°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.30 (br s, 1H, NH), 8.15 (d, *J* = 4.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (s, 1H), 7.39 (s, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.94 (br s, 1H, NH), 6.43 (t, *J* = 4.5 Hz, 1H), 3.57-3.27 (m, 8H), 1.69 - 1.54 (m, 6H), 1.41 (m, 1H), 1.30 (m, 2H), 1.07 (m, 1H).

Example 52

8'-Chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= C-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl], X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

To a suspension of Example 32 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 1-[2-(morpholin-4-yl)-ethyl]-piperazine (64 mg, 0.3 mmol, 0.8 equiv.). After stirring for 2 h, the mixture was diluted with dichloromethane, washed with water and washed with a 1M aqueous solution of sodium hydroxyde. The organic layer was dried over sodium sulfate, concentrated under reduced pressure and the resulting solid was triturated with ethyl acetate/methanol to give 106 mg (50% yield) of the title compound as white solid. mp = 264°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (br s, 1H, NH), 7.75 (m, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.43 (m, 2H), 7.17 (br s, 1H, NH), 3.53 (m, 8H), 2.50-2.36 (m, 12H), 1.84 - 1.78 (m, 6H), 1.63 (m, 1H), 1.56 (m, 2H), 1.29 (m, 1H).

Example 53

8'-Chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= C-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl], X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

To a suspension of Example 32 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 4-[2-(piperazin-1-yl)-acetyl]-morpholine (130 mg, 0.6 mmol, 1.5 equiv.). After stirring overnight, the mixture was diluted with dichloromethane, washed with water and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, concentrated under reduced pressure and the resulting solid was triturated with ethyl acetate/methanol to give 0.1 g (45% yield) of the title compound as white solid. mp =239 °C

^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (br s, 1H, NH), 7.74 (d, *J* = 8.0 Hz, 2H), 7.66 (s, 1H), 7.60 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.17 (br s, 1H, NH), 3.58-3.22 (m, 14H), 2.50 (m, 4H), 1.88 - 1.79 (m, 6H), 1.64 (m, 1H), 1.55 (m, 2H), 1.30 (m, 1H).

Example 54

8'-Chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1= CH, X_2= C-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl], X_3= CH, X_4= C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

To a suspension of Example 32 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 1-hydroxyethylethoxypiperazine (77 mg, 0.4 mmol, 1.1 equiv.). After stirring for 2 h, the mixture was diluted with dichloromethane and washed with water and washed with a 1M aqueous solution of sodium hydroxyde. The organic layer was dried over sodium sulfate, concentrated under reduced pressure to give 0.06 g (29% yield) of the title compound as white solid. mp =100°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (br s, 1H, NH), 7.75 (d, *J* = 8.0 Hz, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.17 (br s, 1H, NH), 4.58 (br s, 1H), 3.59-3.39 (m, 10H), 2.45 (m, 6H), 1.88 - 1.77 (m, 6H), 1.64 (m, 1H), 1.54 (m, 2H), 1.30 (m, 1H).

Example 55

9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-imidazo[2,1-b]quinazoline

formula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X-Z=NCH=CHNH, Y=NH

Preparation of 8'-Chloro-2'-(2,2-dimethoxy-ethylamino)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (intermediate 4)

A solution of Example 7 (1.34 mmol, 0.5 g) in phosphorus oxychloride (7 mL) containing Na_2CO_3 (21 mg, 2 mmol) is heated to 95°C for 4 hours. After cooling to room temperature, the phosphorus oxychloride was removed under reduced pressure. The residue was taken into EtOH (10 mL), amino acetaldehyde dimethyl acetal (1mL, 8.04 mmol) was added and the resulting mixture is refluxed overnight. CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ were added. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/ EtOAc/ MeOH: 80/20/5) to give 0.43 g (96%) of intermediate 4. ^1H NMR [$(CD_3)_2SO$] δ 7.12 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.46 (br s, 1H), 6.08 (br s, 1H), 4.48 (t, *J* = 5.3 Hz, 1H), 3.41 (t, *J* = 5.3 Hz, 2H), 3.32 (m, 6H), 1.72-1.56 (m, 9H), 1.22 (m, 1H).

Preparation of example 55

A solution of intermediate 4 (0.436 g, 1.29 mmol) in a mixture of isopropyl alcohol (10 mL) and 3M aqueous HCl (4 mL) was refluxed overnight. The reaction mixture was allowed to cool to room temperature, was concentrated under reduced pressure and taken into CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude material was recrystallised in EtOAc to afford the title compound as a white solid (0.07 g, 23%) (purity = 95.4%) mp =

197-199°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.58 (br s, 1H), 7.52 (m, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 1.5 Hz, 1H), 2.03 (m, 4H), 1.37-1.45 (m, 6H).

Example 56

9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-[1,2,4]triazolo[3,4-b]quinazoline

formula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X-Z: NCH=NN, Y=NH

Preparation of 8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazolin-2'-yl]-hydrazine

A solution of Example 7 (1.8 mmol, 0.45 g) in phosphorus oxychloride (9 mL) containing Na_2CO_3 (0.28 g, 2.7 mmol) is heated at 95°C for 4 hours. After cooling to room temperature, the phosphorus oxychloride was removed under reduced pressure. The residue was taken into EtOH (10 mL), hydrazine (35% wt. solution in water, 2mL) was added and the resulting mixture was refluxed overnight. CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ were added. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude material (0.43 g, 91%) was used without further purification in the next step. 1H NMR [$(CD_3)_2SO$] δ 7.12 (d, 1H), 7.08 (m, 1H), 6.75 (t, 1H), 1.83-1.60 (m, 7H), 1.47 (m, 2H), 1.25 (m, 1H).

Preparation of example 56

A solution of 8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazolin-2'-yl]-hydrazine (0.58 g, 2.19 mmol), triethyl orthoformate (1.82 mL, 10.95 mmol) and H_2SO_4 (0.05 mL) in butanol (20 mL) was refluxed for 24 h. The reaction mixture was allowed to cool to room temperature, was concentrated under reduced pressure and taken into a mixture of CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The layers were separated, the aqueous one being extracted three

times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude material was recrystallized in EtOAc to afford the title compound as a white solid (0.13 g, 21%).
(purity = 96.6%) mp = 237-239°C.
^1H NMR [$(CD_3)_2SO$] δ 9.99 (br s, 1H), 8.72 (s, 1H), 7.55 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.37 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 2.07 (m, 4H), 1.72 (m, 5H), 1.53 (m, 1H).

Example 57

9'-Chlorospiro[cyclohexane-1-5'-(4',5'-dihydro)]-[1,2,4]triazolo[4,3-a]quinazoline

formula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Y-Z: NCH=NN

To a solution of 8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazolin-2'-yl]-hydrazine (0.35 g, 1.32 mmol) and triethyl orthoformate (1.2 mL, 7.22 mmol) in $CHCl_3$ (16 mL) was added H_2SO_4 (0.04 mL). The mixture was stirred at room temperature for 3 h, was concentrated under reduced pressure and taken into a mixture of CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was taken into butanol (10 mL) and refluxed overnight. After completion, the solvent was evaporated under reduced pressure to give a mixture of 9'-Chlorospiro[cyclohexane-1-5'-(4',5'-dihydro)]-[1,2,4]triazolo[4,3-a]quinazoline and 9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-[1,2,4]triazolo[3,4-b]quinazoline as a 88/12 ratio. Crystallization in CH_2Cl_2 afford the title compound as a white powder (0.045 g, 43%).
(purity = 97.2%) mp = 285-287°C.
^1H NMR [$(CD_3)_2SO$] δ 9.14 (s, 1H), 7.55 (m, 2H), 7.46 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 1.85-1.64 (m, 7H), 1.50 (m, 2H), 1.23 (m, 1H).

Example 58

Spiro[cyclohexane-1-9'-(8',9'-dihydro)-pyrazolo[4',3'-*f*]quinazolin]-7'(6'H)-one

Formula (I): X_1-X_2=C-CH :NNH-C, X_3=CH, X_4=CH, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol A using (N-(1H-indazol-5-yl)urea (1 g, 5.67 mmol), polyphosphoric acid (20 g) and cyclohexanone (0.9 mL, 1.5 equiv.). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/01 to 97/3) followed by recrystallization in toluene to give the title compound as a white solid (14 mg, 1% yield) (purity 98.8%).

^{1}H NMR [$(CD_3)_2SO$] δ 12.97 (br s, 1H, NH), 8.98 (br s, 1H, NH), 8.16 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.70 (br s, 1H, NH), 2.33-2.20 (m, 2H), 1.89-1.78 (m, 4H), 1.68-1.41 (m, 4H).

Example 59

8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of (2-Chloro-5-methoxy-phenyl)-urea (intermediate 5)

A solution of 2-chloro-5-methoxyaniline (5 g, 25.76 mmol) and potassium cyanate (5.22 g, 64.41 mmol) in a mixture of acetic acid (125 mL) and water (12.5 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue taken into a mixture of CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/ EtOAc/ MeOH: 80/20/2) to give 2.06 g (40%) of intermediate 5.

^{1}H NMR [$(CD_3)_2SO$] δ 7.97 (br s, 1H, NH), 7.85 (d, *J* = 3.0 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 6.54 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.4 (br s, 2H), 3.71 (s, 3H).

Preparation of Example 59

Example 59 was prepared according to protocol A using intermediate 5 (1 g, 4.98 mmol), polyphosphoric acid (15 g) and cyclohexanone (0.88 mL, 7.47 mmol). After completion, ice was added, the precipitate was filtered and washed with cold water. The residue was recrystallized in ethanol to afford the title compound as a white powder (0.6 g, 78% yield) (purity 99.54%) mp = 228.5-230.5°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.93 (br s, 1H, NH), 7.27 (d, J = 8.9 Hz, 1H), 7.00 (br s, 1H, NH), 6.65 (d, J = 8.9 Hz, 1H), 3.79 (s, 3H), 2.45-2.38 (m, 2H), 1.84-1.74 (m, 2H), 1.63-1.56 (m, 3H), 1.46 (m, 2H), 1.23-1.13 (m, 1H).

Example 60

5',8'-Difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-F, X_2=CH, X_3=CH, X_4=C-F, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of 2,5-difluorophenyl urea (intermediate 6)

To a solution of 2,5-difluorophenyl isocyanate (1 g, 6.45 mmol) in tetrahydrofuran (50 mL) at 0°C was added a 28% aqueous solution of ammonia (30 mL). The mixture was stirred for 1h allowing the temperature to warm up to room temperature, then concentrated under reduced pressure, taken into water and filtered. The solid was washed twice with water and with ether, then dried at 65°C under reduced pressure to give 740 mg (67%) of intermediate 6.

^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (br s, 1H, NH), 8.02 (m, 1H), 7.21 (m, 1H), 6.72 (m, 1H), 6.29 (br s, 2H, NH_2).

Preparation of Example 60

The title compound was prepared according to protocol A using intermediate 6 (740 mg, 4.3 mmol), polyphosphoric acid (20 g) and cyclohexanone (0.70 mL, 6.75 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 100/0 to 95/5) followed by recrystallization in toluene to give the title compound as a white solid (28 mg, 3% yield) (purity 99%) mp = 194-195°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.26 (br s, 1H, NH), 7.13 (m, 1H), 7.05 (br s, 1H, NH), 6.71 (m, 1H), 2.01 (m, 2H), 1.86-1.75 (m, 4H), 1.64 (m, 1H), 1.49 (m, 2H), 1.18 (m, 1H).

Example 61

8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-CH_3, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of (2-chloro-5-methyl-phenyl)urea (intermediate 7)

A solution of 2-chloro-5-methylaniline (10 g, 70.6 mmol) and potassium cyanate (14.3 g, 176 mmol) in a mixture of acetic acid (340 mL) and water (34 mL) was stirred at room temperature during 4 hours. The solvent was evaporated and the residue taken into a mixture of CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The precipitate was filtered, washed with dichloromethane and dried under vacuum to give 12.6 g (97%) of intermediate 7.

^{1}H NMR [$(CD_3)_2SO$] δ 8.05 (s, 1H, NH), 7.96 (s, 1H), 7.23 (d, 1H), 6.75 (d, 1H), 6.37 (br s, 2H), 2.24 (s, 3H).

Preparation of Example 61

The title compound was prepared according to protocol A using intermediate 7 (12.6 g, 68.2 mmol), polyphosphoric acid (150 g) and cyclohexanone (8.5 mL, 81.9 mmol). After completion, the mixture was poured into ice and water and stirred 45 minutes. The precipitate was filtered and washed with cold water, with diethyl ether and dried under vacuum to give 3.1 g of the title product. The residue (100mg) was recrystallized in ethanol to afford the title compound as a white powder (0.06 g, 17% yield) (purity with HPLC: 99.9%).

^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (br s, 1H, NH), 7.20 (d, J = 8.04 Hz, 1H), 6.89 (br s, 1H, NH), 6.57 (d, J = 8.03 Hz, 1H), 2.47 (s, 3H), 2.02-2.18 (m, 2H), 1.70-1.90 (m, 4H), 1.62-1.70(m, 1H), 1.1.48-1.60 (m, 2H), 1.20-1.35 (m, 1H).

Example 62

8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-CH_2-morpholinyl, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol E. To a stirred solution of Example 7 (1 g, 4 mmol) in glacial acetic acid (15 mL) was sequentially added trioxane (0.55 g, 6 mmol, 1.5 equiv.) and a 48% aqueous solution of hydrobromic acid (5 mL). The mixture was heated to 95°C overnight, poured on ice. The precipitate was filtered, washed twice with water then with ether to give 1.39 g of 8'-Chloro-6'-bromomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid. The crude bromomethyl derivative (150 mg, 0.43 mmol) was treated with morpholine (0.100 mL, 1.1 mmol, 2.6 equiv.) in DMF (3 mL) overnight. The mixture was concentrated under reduced pressure, taken into ethyl acetate, extracted with 1N aqueous HCl. The aqueous layer was washed twice with ethyl acetate, basified to pH 9 and extracted three times with ethyl acetate. The combined organic layers were washed three times with water and brine and concentrated under reduced pressure. The crude material was purified by recrystallization in toluene to give the title compound (102 mg, 68%) (purity 97%) as a white solid. mp = 223°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.33 (br s, 1H, NH), 7.21 (s, 1H), 7.18 (s, 1H), 7.08 (br s, 1H, NH), 3.56 (m, 4H), 3.39 (s, 2H), 2.32 (m, 4H), 1.84-1.49 (m, 9H), 1.25 (m, 1H).

Example 63

8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution

Example 59 (0.83 g, 2.95 mmol) in CH_2Cl_2 (100 mL) boron tribromide (1 N in CH_2Cl_2, 21.8 mL, 21.8 mmol) was added at O°C. The mixture was stirred at room temperature for 48 h, poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by precipitation in Et_2O to afford the title compound as a white solid (0.25 g, 32%). (purity 97.6%) mp = 252-254°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9.90 (br s, 1H), 7.75 (br s, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.97 (br s, 1H, NH), 6.43 (d, *J* = 8.7 Hz, 1H), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.24-1.07 (m, 1H).

Example 64

8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=C-OH, X_2=C-I, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred suspension of Example 63 (10 g, 37.5 mmol) in trifluoroacetic acid (150 mL) at 0 to 5°C was added N-iodosuccinimide (9.47 g, 41.2 mmol) in portions over 10 minutes. The reaction mixture was stirred at 0 to 5°C for 2 hours. The mixture was poured onto a mixture of water (700 mL) and ice (300 mL). The resulting brown solid was filtered and washed with water (250 mL) followed by heptane (4 x 40mL). The solid was pulled dry on the filter bed for 2 hours and then slurried in a mixture of dichloromethane (30 mL) and methanol (5 mL). The dark pink precipitate was filtered and washed with dichloromethane (3 x 20mL) to afford the titled compound (12.2 g, 31.0 mmol, 83%).

^{1}H NMR [$(CD_3)_2SO$] δ 9.10 (s, 1H), 8.25 (s, 1H), 7.81 (s, 1H), 7.18 (s, 1H), 2.70 (m, 2H), 1.95 (m, 2H), 1.75 (m, 3H), 1.60 (m, 2H), 1.28 (m, 1H).

Example 65

8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=C-I, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred suspension of Example 64 (16.27 g, 41.4 mmol) in DMF (325 mL) was added DBU (7.5 mL, 50.1 mmol) followed by methyl iodide (6.8 mL, 109 mmol) at 20 to 25 °C. The reaction mixture was stirred for 3 hours. The mixture was poured into water (1625 mL) and the resulting solid was filtered and washed with water (500 mL) followed by heptane (2 x 150 mL). The solid was stirred in ethyl acetate containing 10% methanol (100 mL) for 10 minutes. The precipitate was filtered and washed with EtOAc (25 mL), TBME (10 mL) and dried *in vacuo* at 50°C to afford the titled compound as a fawn solid (14.4 g, 35.5 mmol, 86%).
^{1}H NMR [$CDCl_3$] δ 7.67 (s, 1H), 7.18 (s, 1H), 5.68 (s, 1H), 3.83 (s, 3H), 2.23 (td, J = 13.6, 4.5, 2H), 1.90 (m, 2H), 1.70 (m, 3H), 1.51 (m, 2H), 1.25 (m, 1H).

Example 66

8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=C-CN, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 65 (3g, 7.38mmol) in NMP (60mL) at 18 to 20°C was added copper (I) cyanide (555mg, 6.2mmol). The mixture was heated to 150°C for 4 days, quenched into ice/water (300mL) and the crude product filtered off. The crude product was dissolved in EtOAc (500mL) and washed with 33% NH_3(aq) solution (2x 200mL). The organic layer was further washed with brine (2x 100mL) and water (2x 100mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo at* 40°C to give the crude product (1.2g, 3.92mmol). The crude product (650mg, 2.12mmol) was purified by preparative HPLC to yield the title compound as a pale yellow solid (97mg, 3.27mmol, 4%) (purity 96%).
^{1}H NMR (360MHz, d^6-DMSO) δ 1.29-1.43 (m, 1H), 1.50-1.70 (m, 2H), 1.73-1.95 (m, 5H), 2.25 (ddd, *J* = 4.5, 13.5 & 13.5Hz, 2H), 4.17 (s, 3H), 5.62-5.68 (br s, 1H), 7.25-7.29 (br s, 1H), 7.54 (s, 1H).

Example 67

8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2CH_2-(4-morpholinyl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (1 g, 3.93 mmol) in DMF (30 mL) under nitrogen at 18 to 20°C was added 60% sodium hydride dispersion (0.16 g, 3.93 mmol). The mixture was stirred for 15 minutes before 4-(2-chloroethyl)morpholine (0.59 g, 3.93 mmol) was added. The mixture was then heated to 100°C for 1.5 hours. After cooling to room temperature the reaction mixture was added to water (300 mL). The resulting solid was filtered and washed with water (50 mL). The crude solid was dried in vacuo at 45°C and subsequent purification by column chromatography (silica 60 g, eluting with 5% methanol in dichloromethane) afforded the title compound (0.48 g, 1.23 mmol, 32%) as a cream solid after drying in vacuo at 50°C.
(purity 96.9%)
^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 6.50 (d, *J* = 8.8 Hz, 1H), 5.65 (s, 1H), 4.10 (t, *J* = 5.5 Hz, 2H), 3.73 (t, *J* = 4.5 Hz, 4H), 2.84 (t, *J* = 5.5 Hz, 2H), 2.68 (td, *J* = 13.5, 4.5 Hz, 2H), 2.56 (t, *J* = 4.5 Hz, 4H), 1.74 (m, 5H), 1.56 (m, 2H), 1.32 (m, 1H).

Example 68

8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 63 (6g, 22.5mmol) in DMF (20mL) at 18 to 20°C was added a solution of potassium carbonate (2M, 9.42mL, 18.84mmol) followed by 2-dimethyl-aminoethyl chloride hydrochloride (2M, 37.7mL, 75.4mmol). The mixture was heated to 100°C for 18 hours and allowed to cool to 18 to 20°C. The reaction mixture was added to water (1.5L) and extracted with EtOAc (2x1L). The

combined organic layer was back washed with water (1L) and separated. The combined organic fractions were dried over with $MgSO_4$, filtered and concentrated *in vacuo at* 40°C to give the crude material (4.7g, 13.9mmol). The crude product was purified by TBME wash (60mL) and charcoal (5g) treatment in DCM (200mL) and column chromatography (silica; gradient elution, 100% EtOAc to 50% in DCM to EtOAc:DCM:MeOH; 2:10:1) to yield the title compound as a pale yellow solid (2.34g, 6.93mmol, 31%) (purity 99%)

^{1}H NMR (360MHz, d^6-DMSO) δ1.21-1.33 (m, 1H), 1.40-1.55 (m, 2H), 1.60-1.72 (m, 5H), 2.29 (s, 6H), 2.57 (ddd, *J* = 4.5, 13.5, 13.5 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H), 4.02 (t, *J* = 6.1 Hz, 2H), 5.48-5.54 (br s, 1H), 6.45 (d, *J* = 9.0 Hz, 1H), 6.92-6.97 (br s, 1H), 7.14 (d, *J* = 9.0 Hz, 1H);

Example 69

8'-Chloro-5'-(2-aminoethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2NH_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of 8'-Chloro-5'-(2-methanesulphonylethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 8)

To a stirred solution of Example 78 (5 g, 1.61 mmol) and triethylamine (1.95 g, 1.93 mmol) in dichloromethane (200 mL) at 0 to 5°C was added a solution of methanesulphonyl chloride (2.21 g, 1.93 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at 20 to 25°C for 5 hours. The mixture was washed with water (2 x 100 mL) and the organic phase was dried over magnesium sulphate. Filtration and concentration *in vacuo* at 40°C afforded intermediate 8 as an off-white solid (5.4 g, 1.39 mmol, 86%).

^{1}H NMR [$CDCl_3$] δ 7.13 (d, J = 9.1 Hz, 1H), 6.99 (s, 1H), 6.38 (d, J = 9.1 Hz, 1H), 5.60 (s, 1H), 4.53 (m, 2H), 4.20 (m, 2H), 3.00 (s, 3H), 2.47 (td, J = 13.6, 4.5 Hz, 2H), 1.59 – 1.78 (m, 5H), 1.48 (m, 2H), 1.28 (m, 1H).

Preparation of Example 69

Intermediate 8 (1.0 g, 2.57 mmol) was stirred with a solution of ammonia in ethanol (40 mL) at 70°C in a sealed pressure vessel for 21 hours. The ethanol was removed by evaporation *in vacuo* at 40°C to leave a fawn coloured solid residue (0.81 g). 2N-Hydrochloric acid (40 mL) was added (no dissolution occurred), the acidic aqueous suspension was treated with 2N-sodium hydroxide to pH 12. The aqueous mixture was extracted twice with ethyl acetate containing 10 % methanol (45 mL and 80 mL). The combined ethyl acetate was washed once with water (50 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo* at 40°C to low volume (10 mL). An off-white solid was filtered off and washed with ethyl acetate (5 mL). The crude amine was purified by column chromatography (silica 20 g, eluting with 20% methanol in dichloromethane) to yield the title compound as an off-white solid after drying *in vacuo* at 50°C (0.30 g, 0.97 mmol, 38%) (purity 98.7%).

^{1}H NMR [$(CD_3)_2SO$] δ 7.80 (br s, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.90 (s, 1H), 6.48 (d, J = 8.8 Hz, 1H), 3.78 (t, J = 5.6, 2H), 2.78 (t, J = 5.6, 2H), 2.40 (m, 2H), 1.65 (m, 2H), 1.25 to 1.51 (m, 7H), 1.01 (m, 1H);

Example 70

8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2NHCH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Intermediate 8 (0.4 g, 1.03 mmol) was stirred with a solution of methylamine in ethanol (27 mL) at 70°C for 7 hours. The ethanol was removed by evaporation *in vacuo* at 40°C and the residue was partitioned between water (25 mL) and ethyl acetate (50 mL), adding 2M-sodium hydroxide (2 mL) to ensure the pH was ≥ 12. The ethyl acetate was washed once with water (15 mL), dried over magnesium sulphate and concentrated *in vacuo* at 40°C to give a pink solid residue. The crude amine was purified by column chromatography (silica 20 g, eluting with 4% triethylamine and 16% methanol in ethyl acetate) to yield the title compound (0.23

g, 0.71 mmol, 69%) as an off-white solid after drying *in vacuo* at 50°C. (purity 99%)

^{1}H NMR (d_6 DMSO) δ 1.21 (m, 1H), 1.54 (m, 2H), 1.68 (m, 3H), 1.85 (m, 2H), 2.41 (s, 3H), 2.58 (m, 2H), 2.95 (t, *J* = 5.7Hz, 2H), 4.08 (t, *J* = 5.7Hz, 2H), 6.70 (d, *J* = 8.9Hz, 1H), 7.12 (s, 1H), 7.31 (d, *J* = 8.9Hz, 1H), 8.02 (s, 1H).

Example 71

8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2OCH_2CH_2NH_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 63 (1.07 g, 4.0 mmol) in DMF (20 mL) at room temperature was added potassium carbonate (1.22 g, 8.8 mmol) and 2-[2-(2-chloroethoxy)ethyl]-1H-isoindole-1,3(2H)-dione (1.22 g, 4.8 mmol). The mixture was heated at 100°C for 8 hours. More potassium carbonate (1.22 g) and 2-[2-(2-chloroethoxy)ethyl]-1H-isoindole-1,3(2H)-dione (1.22 g) were added and the stirred mixture was heated at 100°C for a further 9 hours. After cooling to 18 to 20°C the reaction mixture was added to water (200 mL). The resulting solid was filtered and washed with water (50 mL). The solid was purified by column chromatography (silica 50 g, eluting with 5% methanol in dichloromethane) to yield the phthalimide intermediate (1.0 g, 2.06 mmol, 52%) as a pink glassy solid. To a stirred suspension of the phthalimide intermediate (0.9 g, 1.86 mmol) in ethanol (23 mL) was added hydrazine hydrate (0.28 mL, 5.64 mmol). The mixture was heated at 60°C for 4 hours. 2M-Hydrochloric acid (36 mL) was added and the reaction was heated at reflux for 1.25 hours. Cooling to 18 to 20°C afforded a solid that was isolated by filtration and washed with water (10 mL). The pH of the filtrate was adjusted to 14 by the addition of 2M-sodium hydroxide (2 mL), the crude amine precipitated and was filtered and washed with water (10 mL) and TBME (10 mL). The amine was purified by column chromatography (silica 20 g, eluting with 4% triethylamine and 16% methanol in ethyl acetate) to yield the title compound (0.43 g, 1.21 mmol, 65%) as a white solid after drying *in vacuo* at 50°C. (purity 98%)

^{1}H NMR (360 MHz, d_6 DMSO) δ 1.40 (m, 1H), 1.65 (m, 2H), 1.75 (m, 3H), 2.00 (m, 2H), 2.77 (m, 2H), 2.87 (t, *J* = 5.9Hz, 2H), 3.65 (t, *J* = 5.9Hz, 2H), 3.95 (m, 2H), 4.29 (m, 2H), 6.81 (d, *J* = 9.0Hz, 1H), 7.22 (s, 1H), 7.44 (d, *J* = 9.0Hz, 1H), 8.13 (s, 1H).

Example 72

8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 63 (1.5g, 5.63mmol) in DMF (20mL) at 18 to 20°C was added a solution of potassium carbonate (2M, 9.42mL, 18.84mmol) followed by 3-dimethyl-aminopropyl chloride hydrochloride (1.02g, 6.45mmol). The mixture was heated to 100°C for 18 h. It was then added to water (400mL) and extracted with EtOAc (2x400mL). The combined organic layer was back washed with water (300mL) and separated. Dried with $MgSO_4$, concentrated *in vacuo* at 40°C to give crude material (1.27g, 3.61mmol). The crude product was purified by charcoal (1g) treatment in DCM (120mL) and column chromatography (silica; gradient elution, 100% EtOAc to 50% in DCM to EtOAc:DCM:MeOH; 2:10:1) to yield the desired product as an off white solid (305mg, 0.87mmol, 15%) (purity 99%)

^{1}H NMR (360MHz, d^6-DMSO) δ 1.40-1.53 (m, 1H), 1.65-1.78 (m, 2H), 1.85-2.0 (m, 5H), 2.2 (m, *J* = 7.3, 6.3Hz, 2H), 2.45 (s, 6H), 2.67 (t, *J* = 7.3Hz, 2H), 2.75 (ddd, *J* = 4.6, 13.6 & 13.6Hz, 2H), 4.22 (t, *J* = 6.3Hz, 2H), 5.71-5.75 (br s, 1H), 6.68 (d, *J* = 9.1Hz, 1H), 7.16-7.20 (br s, 1H), 7.35 (d, *J* = 9.1Hz, 1H).

Example 73

8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CO_2CH_2CH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (0.5 g, 1.96 mmol) in DMF (10 mL) at 18 to 20°C was added potassium carbonate (0.6 g, 4.31 mmol) and ethyl bromoacetate (0.36 g, 2.16 mmol). The mixture was heated at 100°C for 1.5 hours, cooled to room temperature and then added to water (100 mL). The resulting solid was filtered and washed with water (50 mL) and heptane (20 mL). Drying in vacuo at 50°C afforded the title compound (0.6 g, 1.7 mmol, 87%) as an off-white solid.

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.2 (d, J = 9.1 Hz, 1H), 7.03 (s, 1H), 6.37 (d, J = 9.1 Hz, 1H), 5.60 (s, 1H), 4.64 (s, 2H), 4.30 (q, J = 7.3 Hz, 2H), 2.70 (td, J = 13.2, 4.1 Hz, 2H), 1.80 (m, 4H), 1.55 (m, 3H), 1.45 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H).

Example 74

5'-Carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2CO_2H, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of potassium hydroxide (0.32 g, 5.65 mmol) in water (1.1 mL) was added to a stirred suspension of the crude Example 73 (0.4 g, 1.13 mmol) in THF (30 mL) at room temperature. The mixture was stirred for 24 hours before the THF was removed by evaporation in vacuo at 40°C. Water (20 mL) was added to the residue and the mixture was washed once with ethyl acetate (10 mL). The aqueous solution was acidified to pH 1 with concentrated hydrochloric acid to afford an off-white solid. The solid was filtered and washed with water (10 mL) and heptane (5 mL). The solid was purified by column chromatography (silica 10 g, eluting with 10% acetic acid in ethyl acetate) to yield the title (0.15 g, 0.46 mmol, 41%) as an off-white solid after drying in vacuo at 50°C.

(purity 98.9%) mp = 284-286°C.

^{1}H NMR [$(CD_3)_2SO$] δ 13.05 (br s, 1H), 7.95 (br s, 1H), 7.24 (d, J = 9.0 Hz, 1H), 6.99 (br s, 1H, NH), 6.54 (d, J = 9.0 Hz, 1H), 4.69 (s, 2H), 2.61 (m, 2H), 1.77 (m, 2H), 1.55 (m, 3H), 1.45 (m, 2H), 1.30 (m, 1H).

Example 75

5'-Carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2CH_2CO_2H$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 63 (1.07 g, 4 mmol) in DMF (20 mL) at 18 to 20°C was added potassium carbonate (1.22 g, 8.8 mmol) and ethyl 4-bromobutyrate (0.82 g, 4.2 mmol). The mixture was heated at 100°C for 2 hours, cooled to room temperature and added to water (200 mL). The mixture was extracted with ethyl acetate (2 x 200 mL). The combined extracts were washed with water (100 mL), dried over magnesium sulfate and evaporated *in vacuo* at 50°C to afford a solid residue. Trituration of the residue with heptane (10 mL) afforded the intermediate ethyl ester (1.27 g, 3.33 mmol, 84%) as a pink solid after drying *in vacuo* at 50°C.

^{1}H NMR (360 MHz, $CDCl_3$) δ 1.11 (t + m, 4H), 1.38 (m, 2H), 1.58 (m, 5H), 2.01 (m, 2H), 2.38 (m, 4H), 3.87 (t, *J* = 5.7Hz, 2H), 4.01 (q, *J* = 6.3Hz, 2H), 5.46 (s, 1H), 6.32 (d, *J* = 8.1Hz, 1H), 6.87 (s, 1H), 7.02 (d, *J* = 8.1Hz, 1H).

6N-Hydrochloric acid (10 mL) was added to a stirred suspension of the ethyl ester (0.9 g, 2.36 mmol) in dioxane (6 mL) at 18 to 20°C. The mixture was stirred under reflux for 2.5 hours. After cooling to 18 to 20°C the solid was filtered and washed with water (50 mL) and TBME (5 mL). The solid was triturated with TBME (30 mL) to afford the title compound (0.64 g, 1.79 mmol, 76%) as an off-white solid after drying *in vacuo* at 50°C. (purity 98%).

^{1}H NMR (360 MHz, d_6 DMSO) δ 1.03 (m, 1H), 1.34 (m, 2H), 1.47 (m, 3H), 1.68 (m, 2H), 1.80 (m, 2H), 2.30 (m, 4H), 3.87 (t, *J* = 6.3Hz, 2H), 6.40 (d, *J* = 9.0 Hz, 1H), 6.90 (s, 1H), 7.11 (d, *J* = 9.0 Hz, 1H), 7.80 (s, 1H), 12.05 (br s, 1H).

Example 76

8'-Chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2CH_2SO_3H$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (1 g, 3.93 mmol) in DMF (20 mL) at 18 to 20°C was added potassium carbonate (1.19 g, 8.65 mmol) followed by sodium 3-bromopropanesulphonate (0.97 g, 4.32 mmol). The mixture was heated at 100°C for 6 hours, cooled to room temperature and then added to water (300 mL). The resulting solution was acidified to pH 1 with concentrated hydrochloric acid. The aqueous mixture was washed with ethyl acetate (200 mL) and evaporated in vacuo to dryness at 70°C. The residue was treated with TBME (200 mL) and a small amount of white solid was filtered and discarded. Decanting away the TBME from the filtrate isolated a pale yellow insoluble oil. Remaining DMF was removed from the oil by further evaporation in vacuo at 70°C. The resulting gum was triturated with acetonitrile (10 mL) to yield the title compound (0.11 g, 0.28 mmol, 7%) as a white solid after drying in vacuo at 50°C.

(purity = 99.7%)

^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 8.27 (br s, 1H), 7.95 (s, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 7.04 (s, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 7.5 Hz , 2H), 2.58 (m, 2H), 2.08 (m, 2H), 1.80 (br m, 2H), 1.60 (br m, 3H), 1.38 (br d, *J* = 12.6 Hz, 2H), 1.22 (m, 1H).

Example 77

8'-Chloro-5'-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2CH_2O-(tetrahydro-pyran-2-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (0.5 g, 1.96 mmol) in DMF (10 mL) at 18 to 20°C was added potassium carbonate (0.6 g, 4.31 mmol) followed by 2-(2-bromoethoxy)tetrahydro-2H-pyran (0.45 g, 2.16 mmol). The mixture was heated at 100°C for 3.2 hours, cooled to room temperature and then added to water (100 mL). The resulting solid was filtered and washed with water (50 mL) followed by

heptane (20 mL). Drying in vacuo at 50°C afforded the title compound (0.69 g, 1.75 mmol, 90%) as an off-white solid.

^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 7.94 (s, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 6.99 (s, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 4.68 (m, 1H), 4.08 (m, 2H), 3.92 (m, 1H), 3.70 (m, 2H), 3.41 (m, 1H), 2.56 (td, *J* = 13.6, 4.1 Hz, 2H), 1.33 – 1.84 (m, 13H), 1.19 (m, 1H),

Example 78

8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2CH_2OH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Example 77 (0.69 g, 1.75 mmol) was stirred in a mixture of THF (20 mL) and water (4 mL). Concentrated hydrochloric acid (0.4 mL) was added and the mixture was stirred at room temperature for 24 h then heated under reflux for 2 hours. The THF was removed by evaporation in vacuo at 40°C and the residue was partitioned between water (25 mL) and ethyl acetate (40 mL). The aqueous phase was separated and extracted with ethyl acetate (20 mL). The combined extracts were washed with water (20 mL), dried over $MgSO_4$ and concentration in vacuo at 40°C afforded the title compound (0.32 g, 1.03 mmol, 59%) as a cream solid after drying in vacuo at 50°C.

(purity = 95.7%) mp = 176-178°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.89 (br s, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 6.98 (br s, 1H, NH), 6.63 (d, *J* = 9.0 Hz, 1H), 4.81 (t, *J* = 5 Hz, 2H), 4.00 (t, *J* = 5 Hz, 2H), 3.76 (q, *J* = 5 Hz, 2H), 2.58 (m, 2H), 1.77 (m, 2H), 1.53 (m, 3H), 1.45 (m, 2H), 1.30 (m, 1H).

Example 79

8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2-(5-ethoxycarbonyl-furan-2-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (0.5 g, 1.87 mmol) and sodium iodide (0.14 g, 1.87 mmol) in DMF (10 mL) at 18 to 20°C was added potassium carbonate (0.258 g, 0.95 mmol) and 5-Chloromethyl-furan-2-carboxylic acid ethyl ester (0.29 mL, 1.87 mmol). The mixture was stirred at room temperature for 2 h. After completion, the solvent was removed under reduced pressure and a mixture of water and EtOAc was added. The layer were separated, the aqueous one being extrated three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The solid was purified by column chromatography (silica 10 g, eluting with CH_2Cl_2/MeOH: 99/1 to 98/2) to yield the title compound (0.75 g, 96%) as a white solid after drying in vacuo at 50°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.98 (br s, 1H, NH), 7.30-7.28 (m, 2H), 7.01 (br s, 1H, NH), 6.80-6.76 (m, 2H), 5.2 (s, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 2.43-2.4 (m, 2H), 1.75-1.72 (m, 2H), 1.56-1.53 (m, 3H), 1.40 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.97 (m, 1H).

Example 80

8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2-(5-carboxy-furan-2-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of lithium hydroxide monohydrate (0.85 g, 20 mmol) in water (1.35 mL), EtOH (11 mL) and MeOH (67 mL) was added to a stirred suspension of the crude Example 79 (0.6 g, 1.43 mmol) in CH_2Cl_2 (17 mL) at room temperature. The mixture was stirred for 48 h before the solvents were removed by evaporation in vacuo at 40°C. Water was added to the residue and the mixture was acidified with concentrated aqueous HCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The solid was purified by column chromatography (silica 5 g, eluting with CH_2Cl_2/MeOH: 70/30) to yield the title compound (0.05 g, 9%) as a white solid after drying in vacuo at 50°C. (purity 98%)

^{1}H NMR [$(CD_3)_2SO$] δ 13.10 (s, 1H), 7.96 (br s, 1H, NH), 7.29 (d, *J* = 9.1 Hz, 1H), 7.12 (br s, 1H, NH), 6.99 (s, 1H), 6.79 (d, *J* = 9.1 Hz, 1H), 6.70 (br s , 1H), 5.15 (s, 2H), 2.43-2.40 (m, 2H), 1.70 (m, 2H), 1.55-1.52 (m, 3H), 1.40 (m, 2H), 0.98-1.00 (m, 1H).

Example 81

8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2CN, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 63 (2 g, 7.85 mmol) in DMF (30 mL) at 18 to 20°C was added potassium carbonate (2.39 g, 17.3 mmol) followed by bromoacetonitrile (1.04 g, 8.64 mmol). The mixture was heated at 100°C for 2 hours, cooled to 18 to 20°C and added to water (300 mL). The resulting solid was filtered and washed with water (60 mL). Drying in vacuo at 50°C afforded crude title compound (2.35 g). The crude product was purified by column chromatography (silica 70 g eluting with 10% methanol in dichloromethane) to yield title compound (1.72 g, 5.6 mmol, 72%) as a fawn solid after drying in vacuo at 50°C.

(purity = 97%) mp = 193-195°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.12 (br s, 1H), 7.36 (d, *J* = 9.0 Hz, 1H), 7.07 (br s, 1H, NH), 6.75 (d, *J* = 9.0 Hz, 1H), 5.24 (s, 2H), 2.34 (m, 2H), 1.80 (m, 2H), 1.63 (m, 3H), 1.47 (m, 2H), 1.20 (m, 1H).

Example 82

8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2-(1H-tetrazol-5-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Example 81 (0.05 g, 0.16 mmol), trimethyltin azide (0.05 mL, 0.179 mmol) and toluene (2 mL) were mixed and refluxed under nitrogen for 15 h. 10M NaOH (0.02

mL, 0.2 mmol) was added and the mixture was stirred at room temperature overnight. The upper layer was removed, hexane was added to the residue, the resulting mixture was stirred for 30 min, hexane was removed. This operation was repeated three times, and EtOAc was added, the precipitate was filtered and washed with EtOAc. The residue was taken into CH_2Cl_2 and 1M HCl (1 mL, 1 mmol) and concentrated under reduced pressure. The precipitate was washed successively with water and MeOH to give the title compound (0.04 g, 71%) as a white powder (purity = 98.1%) mp = 287-289°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.02 (br s, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.01 (br s, 1H), 6.82 (d, *J* = 8.9 Hz, 1H), 5.47 (s, 2H), 2.35 (m, 2H), 1.73 (m, 2H), 1.50 (m, 3H), 1.36 (m, 2H), 0.88 (m, 1H).

Example 83

8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_2-(5-hydroxy-[1,2,4]oxadiazol-3-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of 8'-chloro-5'-(N-hydroxycarbamimidoylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 9)

To a mixture of Example 81 (0.6 g, 1.96 mmol) and hydroxylamine hydrochloride (0.186 g, 2.94 mmol) in ethanol (7 mL) was added sodium hydroxyde (0.114 g, 2.85 mmol) dissolved in the minimum of water. The reaction mixture was heated to reflux for 24h with stirring. After cooling, the solvent was concentrated under reduced pressure. The residue was taken into CH_2Cl_2, the precipitate was filtered, washed with CH_2Cl_2 and dried under vacuum at 45°C to afford intermediate 9 in a quantitative yield.

^{1}H NMR [$(CD_3)_2SO$] δ 9.34 (br s, 1H, OH), 7.94 (br s, 1H, NH), 7.73 (d, *J* = 9.0 Hz, 1H), 6.98 (br s, 1H, NH), 6.70 (d, *J* = 9.0 Hz, 1H), 5.61 (s, 2H), 4.40 (br s, 2H, NH_2), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.24-1.07 (m, 1H).

Preparation of Example 83

To a mixture of intermediate 9 (0.3 g, 0.885 mmol) and ethyl chloroformate (0.13 mL, 1.3 mmol) in anhydrous $CHCl_3$ (4 mL) was added triethylamine (0.22 mL, 1.6 mmol). The reaction mixture was stirred at room temperature for 5 h. After completion, the precipitate was filtered to afford the (ethoxycarbonyl)oxy]amino intermediate (0.275 mg, 76%), which was used directly in the next step without further purification.

^{1}H NMR [$(CD_3)_2SO$] δ 7.98 (br s, 1H, NH), 7.30 (d, *J* = 9.0 Hz, 1H), 6.98 (br s, 1H, NH), 6.78 (br s, 2H, NH_2), 6.70 (d, *J* = 9.0 Hz, 1H), 4.48 (s, 2H), 4.20 (q, *J* = 7.7 Hz, 2H), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.28-1.20 (m, 1H), 1.23(t, *J* = 7.7 Hz, 3H).

A mixture [(ethoxycarbonyl)oxy]amino intermediate (0.275 g, 0.67 mmol) and 1,8-diazabicyclo[5,4,0] undec-7-ene (0.4 mL, 2.67 mmol) in CH_3CN (4 mL) was refluxed for 24h with stirring. The reaction mixture was concentrated under reduced pressure and taken into a mixture of CH_2Cl_2 and aqueous 1M HCl. The layers were separated and the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the title compound (0.17 g, 70%) as a white solid after drying in vacuo at 50°C.

^{1}H NMR [$(CD_3)_2SO$] δ 12.86 (br s, 1H), 8.04 (br s, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.03 (br s, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 5.07 (s, 2H), 2.42-2.36 (m, 2H), 1.78-1.74 (m, 2H), 1.59-1.56 (m, 3H), 1.44 (m, 2H), 1.11 (m, 1H).

Example 84

8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-$OCH_2CH_2N(CH_3)_2$, X_2=C-I, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol L. To a stirred solution of Example 68 (1.5 g, 4.44 mmol) in trifluoroacetic acid (15 mL) were subsequently added N-iodosuccinimide (1.1 g, 4.89 mmol, 1.1 equiv.) and sulfuric acid (4 mL). The resulting solution was stirred for 4 h, and then ethyl acetate and water were

added. The organic layer was separated. The aqueous layer was twice washed with ethyl, basified to pH 9 with 30% aqueous sodium hydroxide then extracted three times with ethyl acetate. The combined organic extracts were washed with water, brine and concentrated under reduced pressure to give 1.95 g (95%) of the title compound as a white solid. (purity 99%)

^{1}H NMR (CDCl3) δ 7.71 (s, 1H), 7.06 (br s, 1H), 5.43 (br s, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 2.82 (t, *J* = 6.0 Hz, 2H), 2.36 (s, 6H), 2.34 (m, 2H), 1.93 (m, 2H), 1.80-1.71 (m, 3H), 1.59-1.50 (m, 2H), 1.33 (m, 1H).

Example 85

6'-(4-Carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=C-(4-carboxyphenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol G. To a stirred solution of Example 65 (7 g, 17.2 mmol) in DMF (84 mL) at 18 to 20°C was added a solution of 4-carboxyphenyl-boronic acid (343 mg, 20.64 mmol) and potassium carbonate (2M, 34 mL, 68 mmol) under N2. After degassing the mixture by bubbling with N2 for 2 h, tetrakis (triphenylphosphine) palladium (1.33 g, 1.147 mmol) was added. The solution was heated to 100°C for 18 h. It was then added to water (1L) and EtOAc (1L). The desired product was precipitated and collected by filtration to give the crude product (3.5 g, 51%). The aqueous filtrate was separated and acidified to pH 1 with concentrated HCl (20 mL). The white solid was collected by filtration (2.7 g, 39%). The crude products were combined and purified by column chromatography (silica 80 g; gradient elution, 20% DCM in EtOAc to 50% DCM in MeOH) to give the title compound (1.77 g, 4.41 mmol, 18%) as an off-white solid. (purity = 99.4%) mp = 309-311°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.27 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.29 (s, 1H), 6.98 (s, 1H), 3.18 (s, 3H), 2.25 (m, 2H), 1.80 (m, 4H), 1.61 (m, 1H), 1.48 (m, 2H), 1.19 (m, 1H).

Example 86

6'-(3-Carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=C-(3-carboxyphenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol G. To a stirred solution of Example 65 (1.75 g, 4.30 mmol) in DMF (30 mL) at 18 to 20°C was added a solution of 3-carboxyphenyl-boronic acid (0.86 g, 5.18 mmol) and potassium carbonate (2M, 8.5 mL, 17mmol) under N2. The mixture was degassed by bubbling N2 for 2 h and tetrakis(triphenylphosphine)palladium (331 mg, 0.286 mmol) was added. The solution was heated to 100°C for 24 h and allowed to cool to 18 to 20°C. The reaction mixture was added to water (200 mL) and EtOAc (300 mL). The desired product was precipitated and collected by filtration, dried in vacuo at 40°C to yield the title compound (567 mg, 1.42 mmol, 33%) as a light brown solid.

(purity = 96%)

^{1}H NMR ($(CD_3)_2SO$) δ 13.06 (br s, 1H), 8.30 (br s, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.01 (br s, 1H), 3.21 (s, 3H), 2.30 (m, 2H), 1.87-1.78 (m, 4H), 1.67-1.64 (m, 1H), 1.53-1.50 (m, 2H), 1.24 (m, 1H).

Example 87

8'-Chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-(2-(4-methyl-piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of (2-bromo-phenyl)-(4-methyl-piperazin-1-yl)-methanone (intermediate 10)

To a solution of 2-bromobenzoyl chloride (2 g, 9 mmol) in toluene (30 mL) was added N-methylpiperazine (2 mL, 18 mmol, 2 equiv.). The resulting mixture was stirred overnight. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was taken into dichloromethane, washed

with water. The organic layer was concentrated under reduced pressure to give 2g (77% yield) of intermediate 10.

^{1}H NMR [CDCl3] δ 7.60 (m, 1H), 7.35 (m, 1H), 7.20 (m, 2H), 3.90-3.80 (m, 2H), 3.40-3.20 (m, 2H), 2.60-2.40 (m, 3H), 2.30 (s, 3H), 2.30-2.25 (m, 1H).

Preparation of Example 87

To a suspension of Example 25 (200 mg, 0.5 mmol) in dimethylformamide (6 mL) were subsequently added sodium acetate (130 mg, 1.6 mmol, 3 equiv.) and bis(pinacolato)diboron (152 mg, 0.6 mmol). The mixture was degassed by bubbling nitrogen and tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol, 0.05 equiv.) was added. The resulting mixture was heated to 45°C overnight and to 90°C for 2 h, concentrated under reduced pressure. The residue was taken into dichloromethane, washed once with water. The organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by flash chromatography on silica gel (heptane/ethyl acetate : 80/20), the resulting solid was hydrolized by hydrochloric acid (1N) in methanol and concentrated under reduced pressure to give 400 mg (66% yield) of the boronic acid. To a suspension of the crude boronic acid (40 mg, 0.14 mmol) in dimethylformamide (2 mL) were subsequently added intermediate 10 (46 mg, 0.16 mmol, 1.2equiv.) and a 2M aqueous solution of potassium carbonate (0.2 mL, 0.4mmol, 3equiv.). The mixture was degassed by bubbling nitrogen and tetrakis(triphenylphosphine)palladium (8 mg, 0.007 mmol, 0.05 equiv.) was added. After heating to 90°C for 3 hours, the mixture was concentrated under reduced pressure, taken into ethyl acetate and washed with water. The organic layer was washed three times with HCl (1N). The aqueous layer was basified to pH 9 and extracted three times with dichlomethane. The organic layer was concentrated under reduced pressure, the resulting solid was crystallized in toluene/methanol to give 10 mg (16% yield) of the title compound as a white solid. mp =250°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.58 (br s, 1H, NH), 7.50-7.49 (m, 2H), 7.43 (m, 1H), 7.33-7.28 (m, 3H), 7.18(br s, 1H, NH), 3.70 (m, 1H), 3.20 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.38 (m, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.86-1.75 (m, 6H), 1.62-1.48 (m, 4H), 1.24-1.16 (m, 2H),

Example 88

8'-Chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-(2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of (4-Bromo-3-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone (intermediate 11)

To a solution of 4-bromo-3-methylbenzoyl chloride (0.5 g, 2 mmol) in toluene (6mL) was added N-methylpiperazine (0.5 mL, 4 mmol, 2 equiv.). The resulting mixture was stirred overnight, The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was taken into ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, concentrated under reduced pressure to give 0.2 g (34% yield) of intermediate 11.

Preparation of Example 88

To a suspension of Example 25 (1 g, 2.5 mmol) in dimethylformamide (25 mL) were subsequently added sodium acetate (650 mg, 8 mmol, 3 equiv.) and bis(pinacolato)diboron (760 mg, 3 mmol, 1.2 equiv.). The mixture was degassed by bubbling nitrogen and tetrakis(triphenylphosphine) palladium (150 mg, 0.13 mmol, 0.05 equiv.) was added . The resulting mixture was heated to 45°C overnight, then additional bis(pinacolato)diboron (635 mg, 2.5 mmol, 1 equiv.) and tetrakis(triphenylphosphine) palladium (100 mg, 0.087 mmol, 0.035 equiv.) was added. The mixture was heated to 90°C overnight and concentrated under reduced pressure. The residue was taken into ethyl acetate, washed once with water. The organic layer was concentrated under reduced pressure and the resulting solid was washed with ethyl acetate to give 0.7g (78% yield) of boronate. To a suspension of the boronate (200 mg, 0.5 mmol) in dimethylformamide (3 mL) were subsequently added intermediate 11 (200 mg, 0.7 mmol, 1.4 equiv.) and sodium acetate (123 mg, 1.5 mmol, 3 equiv.). The

mixture was degassed by bulbbling nitrogen and tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol, 0.05 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, taken into dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (dichloromethane/methanol : 97/3 to 95/5) and the resulting solid was crystallized in toluene/methanol to give 10 mg (6% yield) of the title compound as a white solid. mp = 184° C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (br s, 1H, NH), 7.30-7.23 (m, 5H), 7.15 (br s, 1H, NH), 3.60-3.37 (m, 4H), 2.33-2.27 (m, 7H), 2.20 (s, 3H), 1.78 (m, 6H), 1.62 (m, 1H), 1.5 (m, 2H), 1.24 (m, 1H).

Example 89

8'-Chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-(4-(piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (400 mg, 1.08 mmol) in toluene (4 mL) was added thionyl chloride (0.2 mL, 2.16 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure taken into THF (8 mL). To a 0.135 M solution of the acyl chloride in THF (4 mL, 0.54 mmol) was added triethylamine (0.1 mL, 0.15 mmol, 3 equiv.) and piperazine (70 mg, 0.81 mmol, 1.5 equiv.). After stirring for 2 days, the mixture was concentrated, taken into dichloromethane, washed with water and extracted with a 1N aqueous solution of HCl. The aqueous layer was washed twice with dichloromethane, basified to pH 9 and extracted three times with dichloromethane. The combined organic extracts were concentrated under reduced pressure and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 99/1 to 95/5) to give 181 mg (75% yield) of the title compound as a white solid.

^{1}H NMR [(CD3)$_2$SO] δ 8.54 (br s, 1H, NH), 7.78 (d, *J* = 8.5 Hz, 2H), 7.66 (s, 1H), 7.63 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.17 (br s, 1H, NH), 3.57 (br m, 4H), 2.96 (br m, 4H), 1.88 - 1.77 (m, 6H), 1.64 (m, 1H), 1.54 (m, 2H), 1.28 (m, 1H).

Example 90

8'-Chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-(4-carbamoyl-phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (1g, 2,7 mmol) in toluene (10 mL) was added thionyl chloride (0.4 mL, 5.4 mmol, 2equiv.). The resulting mixture was heated to reflux overnight. The precipitate was isolated by filtration, washed with toluene and dried under reduced pressure to give 0.9 g (90% yield) of the acyl chloride. To a suspension of the acyl chloride (100 mg, 0.25 mmol) in toluene (2 mL) was added a 0.5M solution of ammonia in dioxane (1 mL, 0.5 mmol, 2 equiv.). The mixture was stirred overnight and concentrated under reduced pressure. The residue was taken into dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the resulting solid was purified by flash chromatography on silica gel (dichloromethane/methanol : 97/3) to give 10 mg (66% yield) of the title compound as a white solid. mp =327°C

^{1}H NMR [$(CD_3)_2SO$] δ 8.55 (br s, 1H, NH), 8.02 (br s, 1H, NH), 7.95-7.93 (d, J = 8.5Hz, 2H), 7.80-7.77 (d, J = 8.5Hz, 2H), 7.69 (s, 1H), 7.63 (s, 1H), 7.36 (br s, 1H, NH), 7.17 (br s, 1H, NH), 1.92-1.77 (m, 6H), 1.66-1.63 (m, 1H), 1.55-1.53 (m, 2H), 1.32-1.23 (m, 1H),

Example 91

8'-Chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-(4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a suspension of Example 32 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 hours, and then concentrated under reduced pressure. The

resulting solid was added to a solution of 1-(N-methyl-piperidin-4-yl) piperazine (100 mg, 0.6 mmol, 1.5 equiv.) and triethylamine (0.1 mL, 0.8 mmol, 2 equiv.) in toluene (2 mL). After stirring overnight, the mixture was diluted with dichloromethane and washed with a satured solution of sodium bicarbonate. The organic layer was concentrated under reduced pressure. The resulting solid was washed with ethyl acetate/methanol and crystallized in ethyl acetate/methanol to give 70 mg (33% yield) of the title compound as a white solid. mp =181°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8.53 (br s, 1H, NH), 7.75 (d, *J* = 8Hz, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.43 (d, *J* = 8Hz, 2H), 7.17 (br s, 1H, NH), 3.59-3.31 (br m, 7H), 2.78-2.75 (m, 2H), 2.16-2.12 (m, 4H), 1.88-1.29 (m, 17H).

Example 92

8'-Chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=C-OCH_3, X_2=C-(4-(4-methyl-piperazine-1-carbonyl)phenyl), X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 85 (1 g, 2.55 mmol) in DCM (15 mL) at 18 to 20°C was added a solution of thionyl chloride (0.6 g, 5 mmol) and DMF (0.8 mL). The mixture was stirred at 18 to 20°C for 2 h. The resulting mixture was concentrated *in vacuo at* 55°C. Toluene (10mL) was added to the intermediate and concentrated *in vacuo* at 55°C. (This procedure was repeated to ensure all the unreacted thionyl chloride was removed.). The crude intermediate was dissolved in toluene (10mL) and N-methyl piperazine (0.5g, 5mmol) was added. The reaction was stirred for 15 h at 18 to 20°C and concentrated *in vacuo* at 55°C. The crude product was purified by column chromatography (silica 35g; 60% EtOAc in MeOH) to yield title compound as a pale brown solid (170mg, 0.35mmol, 14%) (purity 95%).

^{1}H NMR [$(CD_3)_2SO$] δ 1.25 (m, 1H), 1.54 (m, 2H), 1.68 (m, 1H), 1.83 (m, 4H), 2.22 (s, 3H), 2.32 (m, 6H), 3.25 (s, 3H), 3.36-3.40 (br s, 2H), 3.56-3.70 (br s, 2H), 7.05-7.09 (br s, 1H), 7.36 (s, 1H), 7.47 (d, *J* = 8.3Hz, 2H), 7.58 (d, *J* = 8.3Hz, 2H), 8.36-8.40 (br s, 1H).

Example 93

8-Chloro-5-methoxyspiro[4H-benzo[d][1,3]oxazin-2-ylamine-4-4'-(tetrahydro-pyran-4'-yl)]

formula (III), X_1=C-OCH_3, X_2=CH, X_3=CH, X_4=C-Cl, A= tetrahydro-pyran-4-yl, X=O, Z^1=NH_2, Y=N

Preparation of N-(2-chloro-5-methoxy-phenyl)-2,2-dimethyl-propionamide (intermediate 12)

To a solution of 2-chloro-5-methoxyaniline hydrochloride (8 g, 41.1 mmol) and triethylamine (12.6 mL, 90.42 mmol) in CH_2Cl_2 (200 mL) under nitrogen pivaloyl chloride (5.57 mL, 45.22 mmol) was added dropwise at 0°C. The reaction mixture was stirred at room temperature overnight. The mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/EtOAc : 98/2) to afford intermediate 12 as a pink oil (7.54 g, 76%).

^{1}H NMR [$CDCl_3$] δ 8.15 (d, *J* = 3.0 Hz, 1H), 8.0 (br s, 1H), 7.17 (d, *J* = 9.0 Hz, 1H), 6.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.79 (s, 3H), 1.33 (s, 9H).

Preparation of N-[6-chloro-2-(4-hydroxy-tetrahydro-pyran-4-yl)-3-methoxy-phenyl]-2,2-dimethyl-propionamide (intermediate 13)

To a stirred solution of intermediate 12 (1 g, 4.13 mmol) in THF (25 mL) under nitrogen at –20°C was added dropwise *n*-butyllithium (2.5M in hexane, 4.13 mL, 10.34 mmol). The reaction mixture was stirred at –10°C for 4 h and *n*-butyllithium (2.5M in hexane, 4.13 mL, 10.34 mmol) was added dropwise at –10°C. The mixture was further stirred for 7 h and tetrahydropyran-4-one was added dropwise at 0°C. The mixture was stirred overnight at room temperature, poured into water and extracted with EtOAc. The organic extracts were washed with saturated aqueous NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude material was purified by precipitation in EtOAc to afford intermediate [illegible] a white powder (0.25 g, 18%).

^{1}H NMR [$CDCl_3$] δ 8.08 (br s, 1H, NH), 7.32 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.95 (t, *J* = 11.5 Hz, 2H), 3.84 (s, 3H), 3.79 (m, 2H), 3.35 (m, 1H, OH), 2.86 (m, 1H), 2.33 (m, 1H), 1.84 (m, 2H), 1.33 (s, 9H).

Preparation of 6-chloro-2-(3,6-dihydro-2H-pyran-4-yl)-3-methoxy-phenylamine (intermediate 14)

A solution of intermediate 13 (0.365 g, 1.06 mmol) and potassium hydroxide (0.24 g, 4.27 mmol) in glycol (0.5 mL) was stirred at 100°C overnight. The reaction mixture was poured into water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography (eluent: cyclohexane/ EtOAc : 90/10) to give title compound (0.187 g, 73%) as a white solid.

^{1}H NMR [$CDCl_3$] δ 7.09 (d, *J* = 9.0 Hz, 1H), 6.24 (d, *J* = 9.0 Hz, 1H), 5.71 (m, 1H), 4.29 (m, 2H), 4.20 (m, 2H), 3.92 (m, 2H), 3.73 (s, 3H), 2.29 (m, 2H).

Preparation of [6-chloro-2-(3,6-dihydro-2H-pyran-4-yl)-3-methoxy-phenyl]-urea (intermediate 15)

A solution of intermediate 14 (0.187 g, 0.78 mmol) and potassium cyanate (0.15 g, 1.95 mmol) in a mixture of acetic acid (5 mL) and water (0.5 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue taken into a mixture of CH_2Cl_2 and an aqueous saturated solution of $NaHCO_3$. The layers were separated, the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give 0.15 g (68%) of crude intermediate 15.

^{1}H NMR [$(CD_3)_2SO$] δ 7.51 (br s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 5.75 (br s, 2H), 5.49 (m, 1H), 4.12 (m, 2H), 3.74 (m, 5H), 2.16 (m, 2H).

Preparation of 8-chloro-5-methoxyspiro[4H-benzo[d][1,3]oxazin-2-ylamine-4-4'-(3'-iodo-tetrahydro-pyran-4'-yl)] (intermediate 16)

A solution of iodine (0.23 g, 0.9 mmol) and sodium iodide (0.2 g, 1.35 mmol) in an aqueous solution of $NaHCO_3$ (10%) (3 mL) was added dropwise to a stirred solution of crude intermediate 15 (0.128 g, 0.45 mmol) in CH_2Cl_2 (5 mL) at room

temperature. After a further 3 h, the reaction mixture was treated with a small amount of $Na_2S_2O_3$. The layers were separated and the aqueous one being extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was precipitate in Et_2O to yield intermediate 16 (0.1 g, 56%) as a white solid after drying in vacuo at 50°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.26 (d, *J* = 8.8 Hz, 1H), 7.17 (br s, 2H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.47 (m, 1H), 4.25 (dd, *J* = 10.3, 2.0 Hz, 1H), 3.97 (m, 1H), 3.82-3.79 (m, 2H), 3.75 (s, 3H), 3.70-3.62 (m, 1H), 1.81 (d, *J* = 14.6 Hz, 1H).

Preparation of Example 93

To a mixture of intermediate 16 (100 mg, 0.24 mmol) and AIBN (0.02 g, 0.12 mmol) in toluene (4 mL) under argon was added tributyltin hydride (0.08 mL, 0.29 mmol). The reaction mixture was heated to 80 °C for 10 h. After completion, the mixture was concentrated under reduced pressure, the residue was taken into CH_3CN and washed three times with hexane. The crude product was purified by flash column chromatography (eluent: CH_2Cl_2/MeOH : 95/5) to give the title compound (31 mg, 46%) as a white solid.

^{1}H NMR [$CDCl_3$] δ 7.22 (d, *J* = 9.0 Hz, 1H), 6.48 (d, *J* = 9.0 Hz, 1H), 5.29 (br s, 2H), 3.88-3.85 (m, 4H), 3.80 (s, 3H), 2.81-2.73 (m, 2H), 1.81 (d, *J* = 14 Hz, 2H).

Example 94

8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=CH; X_3=CH, X_4=C-CF_3, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol A using 2-trifluoromethylphenylurea (500 mg, 2.45 mmol), polyphosphoric acid (3 g) and cyclohexanone (0.3 mL, 2.89 mmol). The crude product was purified by flash chromatography on silica gel (hexane/EtOAc : 100/0 to 50/50) followed by reverse-phase chromatography on a C18 column (water/acetonitrile : 90/10 to 0/100) to give the title compound (13 mg, 2% yield).

^{1}H NMR [$CDCl_3$] δ 7.46 (m, 2H), 7.07 (m, 1H), 7.01 (br s, 1H, NH), 5.60 (br s, 1H, NH), 2.00 (m, 2H), 1.83-1.57 (m, 7H), 1.30 (m, 1H).

Example 95

8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): X_1=CH, X_2=C-CH_2CN, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol E. To a stirred solution of Example 7 (1 g, 4 mmol) in glacial acetic acid (15 mL) was sequentially added trioxane (0.55 g, 6 mmol, 1.5 equiv.) and a 48% aqueous solution of hydrobromic acid (5 mL). The mixture was heated to 95°C overnight, poured on ice. The precipitate was filtered, washed twice with water then with ether to give 1.39 g of 8'-Chloro-6'-bromomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid. The crude bromomethyl derivative (256 mg, 74 mmol) was treated with sodium cyanide (40 mg, 82 mmol, 1.1equiv.) in DMF (10 mL) and was heated to 60°C for two hours. The mixture was concentrated under reduced pressure, taken into water, extracted twice with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified twice by flash chromatography on silica gel (CH_2Cl_2/ MeOH: 99/1 followed by cyclohexane/EtOAc : 60/40 + 2% NH_4OH), to give the title compound (60 mg ,28%) (purity 95%) as a white solid. mp = 239 °C

^{1}H NMR [$(CD_3)_2SO$] δ 8.50 (br s, 1H, NH), 7.30-7.29 (d, 2H), 7.15 (br s, 1H, NH), 3.94 (s, 2H), 1.81-1.68 (m, 7H), 1.54-1.50 (m, 2H), 1.25 (m, 1H).

Example 96

8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=C-$OCH_2CH(OH)CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of 8'-Chloro-5'-(oxiran-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 17)

To a stirred solution of Example 63 (5g, 18.75mmol) in DMF (80mL) at 18 to 20°C was added anhydrous potassium carbonate (6.5g, 46.9mmol) followed by epibromohydrin (2.83g, 20.6mmol) in one portion. The mixture was heated to 80°C for 2 h and then 90°C for 2h. The crude mixture was quenched into water (800ml) and extracted with EtOAc (2x1L). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* at 40°C to give the crude product (3.4g, 57% yield). The crude product was subjected to column chromatography (silica 100g, eluting with 30% to 50% EtOAc in heptane) to afford intermediate 17 (2.7g, 45% yield) as a white solid after drying *in vacuo* at 45°C (purity 98.9%).

^{1}H NMR [$CDCl_3$] δ 6.96 (d, *J* = 8.8 Hz, 1H), 6.76-6.79 (br s, 1H), 6.24 (d, *J* = 8.8 Hz, 1H), 5.30-5.35 (br s, 1H), 4.09 (dd, *J* = 2.8, 10.9 Hz, 1H), 3.67 (dd, *J* = 6.3, 10.9 Hz, 1H), 3.16 (m, 1H), 2.73 (dd, *J* = 4.3, 4.8 Hz, 1H), 2.53 (dd, *J* = 2.5, 4.8 Hz, 1H), 2.28-2.38 (m, 2H), 1.45-1.61 (m, 5H), 1.23-1.36 (m, 2H), 1.04-1.15 (m, 1H).

Preparation of example 96

To a stirred solution of dimethylamine in EtOH (17mL, 5.6M, 95.2mmol) at 18 to 20°C was added intermediate 17 (730mg, 2.26mmol) in one portion. The mixture was heated to 40°C for 2.6 h. The solid was filtered, washed with EtOH (40mL) and dried *in vacuo* at 40°C to yield the desired product as a white solid (515mg, 1.40mmol, 62%)(purity 99%).

^{1}H NMR [$(CD_3)_2SO$] δ 7.10 (d, *J* = 9.0 Hz, 1H), 6.90-6.94 (br s, 1H), 6.42 (d, *J* = 9.0 Hz, 1H), 5.44-5.50 (br s, 1H), 3.99 (m, 1H), 3.91 (m, 2H), 3.50-3.54 (br s, 1H), 2.52 (m, 3H), 2.33 (dd, *J* = 12.1, 3.5 Hz, 1H), 2.27, (s, 6H), 1.59-1.76 (m, 5H), 1.38-1.52 (m, 2H), 1.18-1.30 (m, 1H).

Example 97

8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=C-$OCH_2CH(OH)CH_2NHCH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of methylamine in EtOH (12mL, 8M, 96mmol) at 18 to 20°C was added intermediate 17 (500mg, 1.55mmol) in one portion. The mixture was heated to 40°C for 2 h. A further portion of methylamine in EtOH (10mL, 8M, 80mmol) was added and the reaction heated at 40°C for another 20mins. The mixture was concentrated *in vacuo* at 40°C and TBME (30mL) was added. The white solid (390mg, 1.1mmol) formed was filtered to give the crude product (390mg, 1.1mmol). The material was dissolved in DCM (20mL) and heated to 35°C for ten minutes in the presence of charcoal (2g). The suspension was filtered through a pad of celite, washed with DCM (20mL) and concentrated *in vacuo* at 40°C to yield the title compound as a white solid (200mg, 36% yield) (purity 97.3%).

^{1}H NMR [$(CD_3)_2SO$] δ 7.21 (d, *J* = 9.0 Hz, 1H), 7.00-7.06 (br s, 1H), 6.54 (d, *J* = 9.0 Hz, 1H), 5.55-5.59 (br s, 1H), 4.04 (m, 2H), 4.13 (m, 1H), 2.90 (dd, *J* = 3.8, 12.0 Hz, 1H), 2.80 (dd, *J* = 8.4, 12.0 Hz, 1H), 2.60 (m, 2H), 2.54 (s, 3H), 2.05-2.25 (br s, 2H), 1.70-1.88 (m, 5H), 1.48-1.63 (m, 2H), 1.25-1.38 (m, 1H).

Example 98

8'-Chloro-5'-[2-(ethoxycarbonylmethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X_1=C-$OCH_2CH_2NHCH_2COOCH_2CH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred suspension of intermediate 8 (2.0g, 5.14mmol) in acetonitrile (28mL) was added a solution of ethyl glycinate (3.72g, 3.6mmol) in acetonitrile (12mL). The mixture was stirred under reflux for 24 hours. Concentration *in vacuo* at 40°C afforded an orange oil (5g) which was subjected to column chromatography (silica 110g, eluting with 50% to 100% EtOAc in heptane followed by 90% EtOAc in DCM) to give the title compound (450mg, 22% yield) as a white solid after drying *in vacuo* at 45°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7.94-7.98 (br s, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.01-7.05 (br s, 1H), 6.62 (d, *J* = 9.0 Hz, 1H), 4.08 (t, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 5.6 Hz, 2H), 3.41 (s, 2H), 2.95 (t, *J* = 5.6 Hz, 2H), 2.45-2.55 (m, 2H), 2.12 (br s, 1H), 1.70-1.85

(m, 2H), 1.52-1.63 (m, 3H), 1.40-1.49 (m, 2H), 1.21-1.25 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H).

Example 99

8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride

X_1=C-$OCH_2CH_2NHCH_2COOH$, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

To a stirred solution of Example 98 (600mg, 1.52 mmol) in 1,4-dioxane (8mL) was added a solution of HCl (6N, 10.5mL) at 18 to 20°C. The reaction mixture was heated to 90°C for 2 h. It was then quenched onto water (100mL) and washed with DCM (200mL). The aqueous layer was concentrated and dried *in vacuo* at 60°C to give title compound (614mg, 99.9% yield) as a white solid (purity 95.9%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (d, J = 9.1 Hz, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.17 (t, J = 5.6 Hz, 2H), 3.86 (s, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.24-2.34 (m, 2H), 1.40-1.60 (m, 7H), 1.15-1.26 (m, 1H).

Biological results

In vitro inhibition of the phosphodiesterase 7 and of other phosphodiesterases

The capacity of the compounds of the invention to inhibit cyclic nucleotide phosphodiesterases was evaluated by measuring their IC_{50} (concentration necessary to inhibit the enzymatic activity by 50 %).

PDE3A3, PDE4D3, PDE7A1 were cloned and expressed in insect cells Sf21 using the baculovirus expression system and we uses directly the cell culture supernatant as enzyme source. The source of PDE1 and of PDE5 were human cell lines (respectively TPH1 human monocytes and MCF7 human caucasian breast adenocarcinoma).

They were obtained partially purified on an anion exchange column (Mono Q) according to a method adapted from Lavan B.E.,Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

Measurement of the enzymatic activity for the various types of PDE was then made according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY. The substrate used was cGMP for PDE1 and PDE5 and cAMP for PDE 3, PDE 4 and PDE 7. The substrate concentration was 0.2µM for PDE 1, PDE 3 and PDE 5, 0,25µM for PDE 4 and 50nM for PDE 7.

The enzymatic reaction was stopped after 1 hour for PDE 1, PDE 3 and PDE 5 and 10 minutes for PDE 4 and PDE 7.

In order to determine their IC_{50}, compounds of the invention were assayed at 8 to 11 concentrations ranging from 0.02nM to 100µM for PDE 4 and PDE 7 and at least at 6 concentrations ranging from 0,1µM to 30µM for PDE 1, 3 and 5.

The IC_{50} (µM) were determined for some of the compounds of the invention, and the IC_{50} of most of the compounds of examples 1 to 99 were comprise between 0.008 µM and 18 µM.

The activity of some of the most active compounds are summarized in the following table:

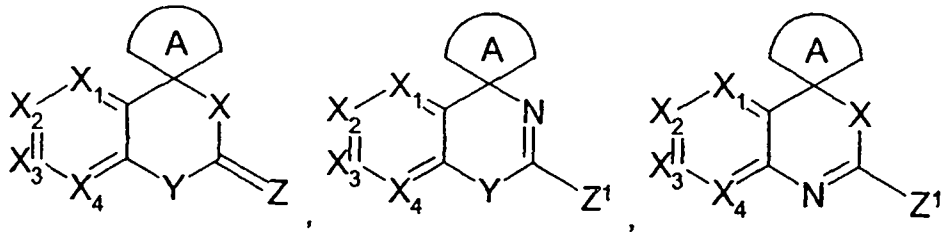
Example number	IC_{50} PDE7 (µM)
15	0,014
26	0,016
34	0,012
38	0,018
41	0,02
51	0,008
52	0,015
53	0,013
54	0,013

These results show that the compounds of the invention inhibit PDE7 at very low concentrations, with some IC_{50} values lower than 100nM. The results of the assays with other PDE (1, 3, 4 and 5) show IC_{50} values often superior to 1µM or even 10 µM.

It demonstrates that compounds of the invention are strong and selective PDE7 inhibitors.

Claims

1. Compounds having the following formula (I), (II) or (III),



(I) (II) (III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, , the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group,

these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;

  these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)$-NH-SO_2-CH_3, CF_3, OR^6, $COOR_6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2, or N, and which may be substituted with,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl,

OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from $CH\text{-}NO_2$, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{10}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is $N\text{-}R^{12}$ and Z is $N\text{-}R^{13}$, may form together a -CH=N- group or a -C=C- group,
- when X is $N\text{-}R^{9}$ and Z is $N\text{-}R^{13}$, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

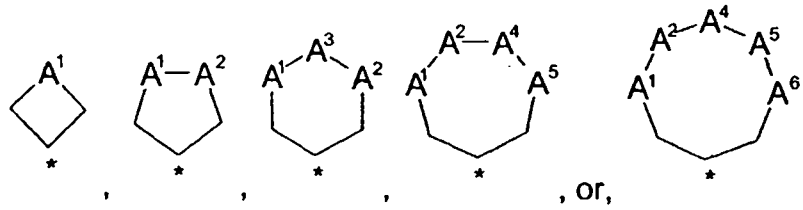
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , , or,

in which,

- A^1, A^2, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- A^3 is selected from O, S, C, C(=O), SO or SO_2, or N-R^{18} when A^1 and/or A^2 are C(=O) or when Y is O or S, wherein R^{18} is as defined above;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that:

- not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;
- the cycle A does not contain more than 2 carbon atoms in an sp^2 hybridization state;
- when X is O, X_2 is not C-R^1 in which R^1 is
  - a thienyl substituted with CN or with CN and CH_3,
  - a phenyl substituted with CN, Cl, NO_2 or CN and F,
  - Br
  - F;

or their tautomeric forms, their racemic forms or their isomers and their pharmaceutically acceptable derivatives.

2. A compound of formula (II) or (III) according to claim 1, in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:

- halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with
    - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
    - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from
      - H, or,
      - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

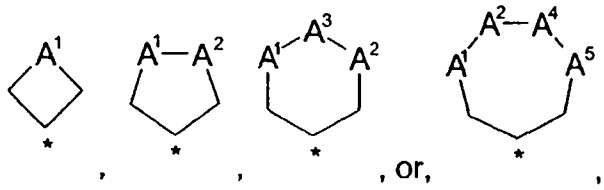
e) Z^1 is chosen from $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14},
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14} or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

3. A compound of formula (I) in which X_1, X_2, X_3, X_4, X, Y, Z and A are as defined in claim 1.

4. A compound of formula (I) according to claim 3 in which

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:
  - halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
    - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in

which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with,
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

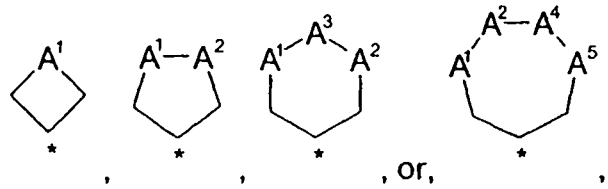
b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

e) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,

- an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

5. A compound of formula (I), according to claim 1 in which, X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X^5-R^5 in which,
  - X^5 is selected from :
    - a single bond,
    - a lower alkylene, optionally interrupted with 1 heteroatoms chosen from O, S and N
  - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,

- lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
  - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower alkyl;
  - n is an integer selected from 0, 1, 2, 3 or 4;
- these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, CF_3, $C(=O)NH\text{-}SO_2CH_3$, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

6. A compound of formula (I) according to claim 5, in which X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 fluor atoms, OR^3, $COOR^3$ or NR^3R^4 in which R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl;

  R^3 and R^4 together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X^5-R^5 in which X^5 is a single bond and R^5 is selected from aryl, heteroaryl, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3,

in which Q1 and Q3 are the same or different and are selected from

- hydrogen, halogen, CN, lower alkyl,
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ or $SO_2NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl, Q4-heteroaryl in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 0, 1, 2 or 3;

    these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO_3H, $C(=O)$-NH-SO_2-CH_3, OR^6, $COOR^6$ or NR^6R^7, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which

may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

7. A compound of formula (I) according to claim 5, in which, X_1 is C-R^1, in which R^1 is selected from

- hydrogen, halogen, OR^2, COR^2, $COOR^2$,$CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from
  - hydrogen,
  - lower alkyl, Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl;
    - n is an integer selected from 0, 1, 2 or 3;

  these groups being unsubstituted or substituted with lower alkyl, CN, OR^6, SO_3H, C(=O)-NH-SO_2-CH_3, $CONR^6R^7$, $COOR^6$, COR^6 or NR^6R^7, in which and R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2, COOH, OH ;

R^6 and R^7 together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with ,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- COR' or lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;

- lower alkyl optionally substituted with CN, SO_3H, OR^3, NR^3R^4, $COOR^3$ or $CONR^3R^4$ in which R^3 and R^4 are the same or different and are selected from
  - hydrogen and,
  - lower alkyl optionally substituted with OH, COOH or NH_2

- the group X^5-R^5 in which X^5 is a lower alkylene optionally interrupted with a heteroatom selected from O and N and R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N and cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N,
these groups being unsubstituted or substituted OR^3 or $COOR^3$ in which R^3 is selected from hydrogen and lower alkyl;
R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - C(=O)-R' or a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from hydrogen or lower alkyl.

8. A compound of formula (I) according to claim 5 in which, X_1 is C-R^1, in which R^1 is selected from hydrogen, halogen or OR^2 in which R^2 is selected from

- hydrogen,
- lower alkyl, unsubstituted or substituted with CN, C(=O)-NH-SO_2-CH_3, OR^6, SO_3H, $COOR^6$ or NR^6R^7;
- Q4-oxadiazole, Q4-tetrazole, Q4-morpholine, Q4-furan, Q4-isoxazole, in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 1 and 2;

these groups being unsubstituted or substituted with CH_3, OR^6 or $COOR^6$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2 or COOH.

9. A compound of formula (I) according to any one of claims 5, 7 and 8 in which X_2 is C-R^1, in which R^1 is X^5-R^5, in which

- X^5 is a single bond,
- R^5 is phenyl or pyridyl,
  - optionally substituted with a lower alkyl, and,
  - substituted with C(=O)NR^3R^4 in which R^3 and R^4 together with the nitrogen atom to which they are linked, form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

10. A compound of formula (I) according to any one of claims 5 to 9 in which one of X_1, X_2, X_3 and X_4 is C-R^1 in which R^1 is hydrogen while the others are identical or different and are C-R^1 in which R^1 is other than hydrogen.

11. A compound of formula (I) according to claim 10, in which X^3 is C-R^1 in which R^1 is hydrogen.

12. A compound of formula (I) according to any one of claims 5 to 10, in which X_3 is C-R^1, in which R^1 is selected from :

- hydrogen or halogen, or,
- X^5-R^5 in which R^5 is a single bond and R^5 is aryl or heteroaryl, optionally substituted with one, two or three groups which are the same or different and which are selected from halogen, CN, CF_3, SO_2Me, OR^2, $COOR^2$, NR^2R^3, $SO_2NR^2R^3$ and $CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl.

13. A compound of formula (I) according to claim 12 in which X_3 is C-R^1, in which R^1 is selected from hydrogen or halogen.

14. A compound of formula (I) according to any one of claims 5 to 13 in which X_4 is C-R^1, in which R^1 is selected from

- hydrogen, halogen, CF_3, O-lower alkyl, $COOR^2$ or,
- lower alkyl optionally substituted with OR^2, $COOR^2$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl.

15. A compound of formula (I) according to any one of claims 5 to 14 in which X is NH.

16. A compound of formula (I) according to any one of claims 5 to 15 in which Y is NH.

17. A compound of formula (I) according to any one of claims 5 to 16 in which Z is O or N-CN.

18. A compound of formula (I) according to any one of claims 17 in which Z is O.

19. A compound of formula (I) according to any one of claims 5 to 18 in which A is selected from cyclohexyl or cycloheptyl, optionally interrupted with C(=O) or O, and unsubstituted or substituted with CH_3, OH or OCH_3.

20. A compound of formula (I) according to any one of claims 5 to 19 in which A is selected from unsubstituted cyclohexyl or cycloheptyl.

21. A compound of formula (I), (II) or (III) according to any one of claims 1 to 20 wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond

22. A compound selected from the group consisting of
Spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
Spiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',7'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Bromospiro[cyclobutane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromo-4-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one
8'-chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-thione
8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline
8'-Chloro-2'-methoxyiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline,
8'-Chloro-2'-dimethylaminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline],
8'-Chloro-1'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-1'-(ethoxycarbonylmethyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-Chloro-3'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-imidazo[2,1-b]quinazoline
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-[1,2,4]triazolo[3,4-b]quinazoline,
9'-Chlorospiro[cyclohexane-1-5'-(4',5'-dihydro)]-[1,2,4]triazolo[4,3-a]quinazoline,
Spiro[cyclohexane-1-9'-(8',9'-dihydro)-pyrazolo[4',3'-f]quinazolin]-7'(6'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-aminoethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8-Chloro-5-methoxyspiro[4H-benzo[d][1,3]oxazin-2-ylamine-4-4'-(tetrahydro-pyran-4'-yl)],
8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(ethoxycarbonylmethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

23. A compound selected from the group consisting of
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

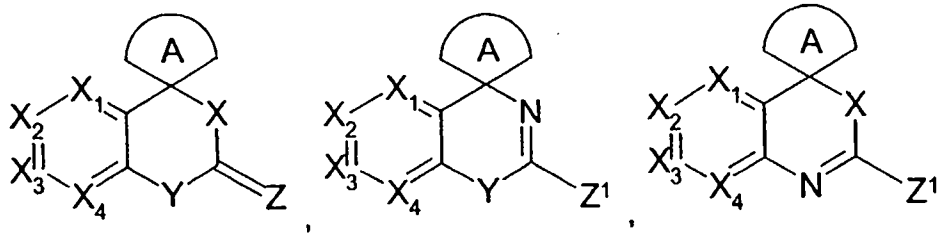
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl] spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, and,
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

24. A compound according to any one of claim 1 to 23 for use as a medicament

25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 in combination with an appropriate carrier.

26. Use of a compound of formula (I), (II) or (III),



(I) (II) (III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:
- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group,

these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)$-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;

  these groups being unsubstituted or substituted with one or several groups selected from halogen, lower alkyl, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)$-NH-SO_2-CH_3, CF_3, OR^6, $COOR_6$, $C(=O)R_6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O, S or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with

1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is N-R^{12} and Z is N-R^{13}, R^{12} and R^{13} may form together a -CH=N- group or a -C=C- group,
- when X is N-R^9 and Z is N-R^{13}, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

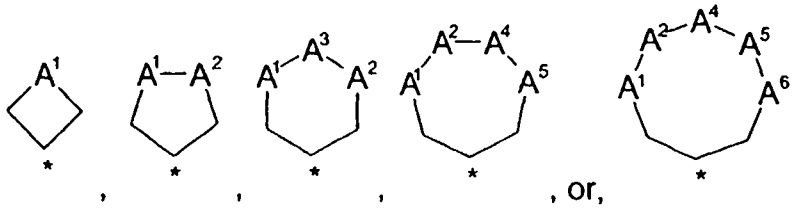
- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or

two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , or,

in which,

- A^1, A^2, A^3, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;

of their tautomeric forms, their racemic forms or their isomers and of their pharmaceutically acceptable derivatives,

for the preparation od a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

27. Use according to claim 26 in which said compound is a compound of formula (I) in which X_1, X_2, X_3, X_4, X, Y, Z and A are as defined in claim 25.

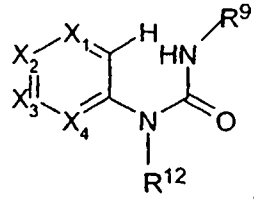
28. Use of a compound according to any one of claims 1 to 23 for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

29. Use according to any one of claims 26 to 28 in which said disorder is selected from T-cell-related diseases, autoimmune diseases, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease, asthma, cancer, acquired immune deficiency syndrome, allergy or inflammatory bowel disease.

30. A method for the prevention or the treatment of a disorder for which a therapy by a PDE7 inhibitor is relevant , comprising administering to a mammal in need thereof, an effective amount of a compound according to any one of claims 1 to 23.

31. A method according to claim 30 in which said disorder is selected from T-cell-related diseases, autoimmune diseases, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease, asthma, cancer, acquired immune deficiency syndrome, allergy or inflammatory bowel disease.

32. A method for preparing a compound of formula (I) according to claim 1 in which Y is N-R^{12}, X is N-R^9 and Z is O comprising reacting a substituted urea of formula



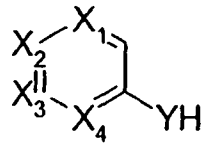
in which X_1, X_2, X_3, X_4, R_9 and R_{12} are as defined claim 1, with a cyclic ketone of formula



in which A is as defined in claim 1, to obtain said compound of formula (I) and isolating said compound of formula (I).

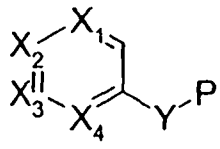
33. A method for preparing a compound of formula (I) according to claim 1 in which X_1, X_2, X_3, X_4, A and R^9 are as defined in claim 1 and Y is O, S or NH, said method comprising,

(1) reacting a compound (2a)



(2a)

in which X_1, X_2, X_3, X_4 are as defined in claim 1 and Y is O, S or NH, with a group P-LG in which P is a protecting group and LG is a leaving group to obtain compound (2b)

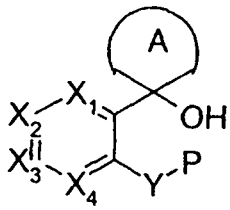


(2b)

(2) reacting compound (2b) with R-Li in which R is lower alkyl and then with a ketone of formula

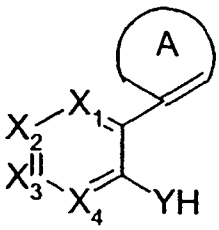


in which A is as defined in claim 1 to obtain compound (2c)



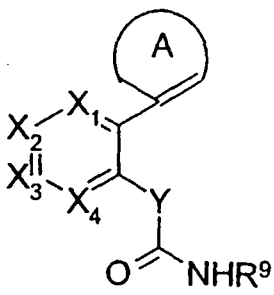
(2c)

(3) removing the protecting group P either under reductive conditions, acidic condition or basic condition to obtain compound (2d)



(2d)

(4) reacting compound (2d) with a group O=C=N-R^9 in which R^9 is as defined in claim 1 to obtain compound (2e)



(2e)

(5) reacting compound (2e) with an acid to obtain said compound of formula (I),

(6) isolating said compound of formula (I).

DERIVADOS ESPIROCÍCLICOS NUEVOS Y SU USO COMO INHBIDORES DE FOSFODIESTERASA-7

Campo de la Invención

La invención se relaciona con derivados espirocíclicos, el proceso para su preparación, y su uso como inhibidores de fosfodiesterasa 7 (PDE7).

Antecedentes de la Invención

Las fosfodiesterasas (PDE) juegan un importante papel en diversos procesos biológicos hidrolizando los segundos mensajeros clave monofosfatos 3',5'-cíclicos de adenosina y guanosina (cAMP y cGMP respectivamente) en sus nucleótidos de 5'-monofosfato correspondientes. En consecuencia, la inhibición de la actividad de PDE produce un aumento de los niveles intracelulares de cAMP y cGMP que activan las vías de fosforilación de proteína específicas involucradas en una variedad de respuestas funcionales.

Por lo menos once isoenzimas de fosfodiesterasas nucleótidas cíclicas de mamíferos, numeradas de PDE 1 a PDE 11, han sido identificadas sobre la base de la estructura principal,

especificidad del sustrato y sensibilidad a cofactores o drogas inhibidoras.

Entre estas fosfodiesterasas, PDE7 es una PDE específica de cAMP. La caracterización bioquímica y farmacológica mostró una PDE específica de cAMP de alta afinidad (Km=0,2 μM), que no fue afectada por los inhibidores de isoenzimas de PDE selectivos potentes de cGMP.

Se ha detectado actividad o proteína de PDE7 en cultivos de células T, cultivos de células B, cultivos de células epiteliales de las vías respiratorias (AE) y varios tejidos fetales.

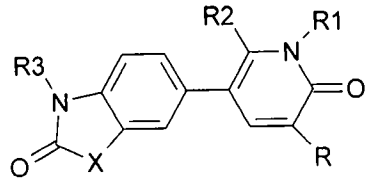
El incremento de los niveles de cAMP mediante la inhibición de PDE7 selectiva parece ser un enfoque potencialmente prometedor para bloquear específicamente respuestas inmunes mediadas por células T. Otros estudios han demostrado que la elevación de los niveles de cAMP intracelular puede modular los procesos inflamatorios e inmunológicos. Este enfoque selectivo podría presumiblemente exento de los efectos colaterales asociados con inhibidores de PDE selectivos conocidos (ej. inhibidores selectivos de PDE3 o PDE4) y que limitan su uso.

También se ha revelado un rol funcional de PDE7 en la activación de las células T; en consecuencia los inhibidores de PDE7 selectivos serían candidatos para el tratamiento de enfermedades relacionadas con las células T.

Las células AE participan activamente en enfermedades inflamatorias de las vías respiratorias liberando mediadores tales como metabolitos y citocinas de araquidonato. La inhibición selectiva de PDE7 puede ser un enfoque antiinflamatorio útil para tratar enfermedades relacionadas con células AE.

Por lo tanto, existe una necesidad de inhibidores selectivos de PDE7, que son activos a muy bajas concentraciones, es decir preferentemente inhibidores nanomolares.

WO 88/01508 revela compuestos de la fórmula



donde R es hidrógeno, alquilo, alcoxialquilo, hidroxialquilo, halo, ciano, carbamoilo, alquil carbamoilo, formilo, alquilamino o amino;

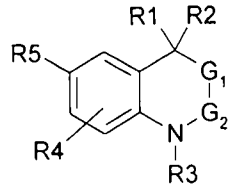
X es $-(CR^4R^5)_a-NR_6-(CR^4R^5)_b$;

R^1, R^2, R^3 y R^5 son hidrógeno o alquilo;

R^4 y R^6 son hidrógeno, alquilo o aralquilo; a y b son 0, 1, o 2 y a + b = 0, 1 o 2;

los grupos de R^4 y R^5 sobre átomos de carbono vecinos pueden juntos formar un enlace doble de carbono-carbono; y los grupos geminales de R^4 y R^5 pueden juntos formar un sustituyente espiro, $-(CH_2)_d$, donde d es de 2 a 5; o una sal farmacéuticamente aceptable de ellos. Estos compuestos se describen como cardiotónicos.

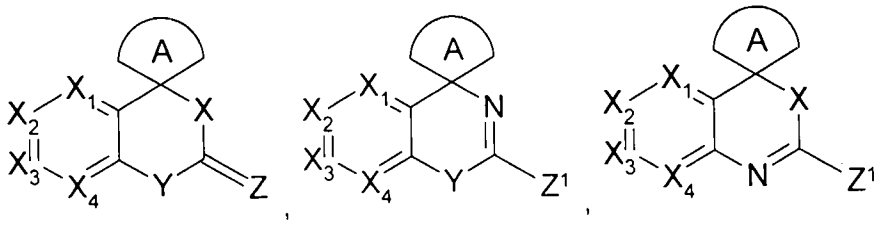
WO 00/66560 revela compuestos de la fórmula



Estos compuestos se describen como moduladores de receptores de progesterona.

Resumen de la Invención

La invención proporciona el uso de derivados espirotricíclicos, que son inhibidores de PDE y más particularmente inhibidores de PDE7, que tienen las siguientes fórmulas (I), (II) o (III):



(I) (II) (III)

en donde:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

-C-R^1, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,
    - alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o =N-R^6 en donde R^6 y R^7 son iguales o

diferentes y se seleccionan de hidrógeno o alquilo inferior, y

- R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno, CN, SO_2NH_2 o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
- hidrógeno,
- alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-

cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde

- Q_4 se selecciona de $(CH_2)_m$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR', NR'R" en donde R' y R" son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- n es un número entero seleccionado de 0, 1, 2, 3, o 4;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, C(=O)-NH-C(=O)NR^6R^7 o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

- $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que pueden contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de
- H o
- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S o N; o

- cuando X_1 y X_2 ambos representan C-R^1, los sustituyentes R^1 pueden formar junto con los átomos de carbono al cual están unidos, un anillo heterocíclico de 5 miembros que comprenden un átomo de nitrógeno y optativamente un segundo heteroátomo seleccionado de O, S o N;

b) X es O, S o NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos compuestos son no sustituidos o

sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de CH-NO_2, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos

elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,

- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14}, $COOR^{14}$ o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, puden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior o

- cuando Y es $N-R^{12}$ y Z es $N-R^{13}$, R^{12} y R^{13} pueden formar juntos un grupo -CH=N- o un grupo -C=C-,
- cuando X es $N-R^{9}$ y Z es $N-R^{13}$, R^{9} y R^{13} pueden formar juntos un grupo -CH=N- o un grupo -C=C-;

e) Z^1 se elige de H, CH_3 o $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

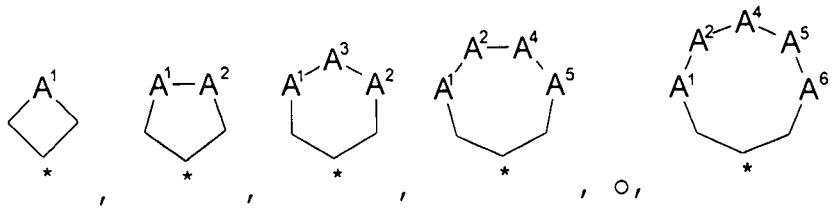
- hidrógeno, CN, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos

elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,

- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14}, $COOR^{14}$ o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior y R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o más heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior;

f) A es un ciclo elegido de:



en donde

- A^1, A^2, A^3, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,

- alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior, y
R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

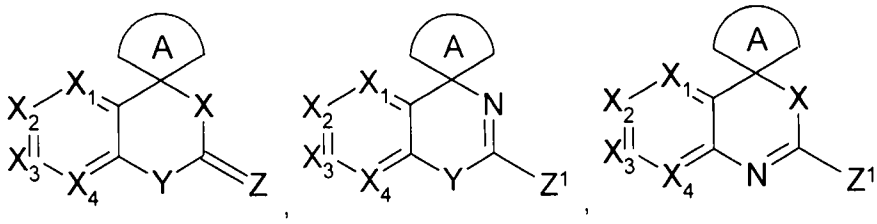
- 2 átomos del ciclo A, que no son adyacente, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;

o sus formas tautoméricas, sus formas racémicas o sus isómeros y sus derivados farmacéuticamente aceptables,

para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

La invención también se relaciona con compuestos, que son inhibidores de PDE7, que tienen la siguiente fórmula (I), (II) o (III):



(I) (II) (III)

en donde

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 simultáneamente representen un átomo de nitrógeno, o,
- C-R^1, en donde R^1 se selecciona de:
  - Q_1, o

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- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde

-X^5 se selecciona de:

- un solo enlace;
- alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S o =N-R^6 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y
- R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de:

- hidrógeno, halógeno, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno, CN, SO_2NH_2 o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR' o NR'R'' en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;
    - n es un número entero seleccionado de 0, 1, 2, 3 o 4;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)-NH-SO_2-CH_3$, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior, y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2, o N, y pueden ser sustituidos con
  - $(CH_2)_n-Q_5$, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
  - un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o,
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, puede formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o,

- cuando X_1 y X_2 ambos representan C-R^1, los 2 sustituyentes R^1 pueden formar junto con los átomos de carbono a los cuales están unidos, un anillo heterocíclico de 5 miembros que comprende un átomo de nitrógeno y optativamente un segundo heteroátomo seleccionado de O, S o N;

b) X es O o NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de $CH-NO_2$, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14}, $COOR^{10}$ o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos

elegidos de O, S o N, y que pueden ser sustituidos con un alquilo inferior o

- cuando Y es N-R^{12} y Z es N-R^{13}, pueden formar juntos un grupo -CH=N- o un grupo -C=C-,
- cuando X es N-R^9 y Z es N-R^{13}, R^9 y R^{13} pueden formar juntos un grupo -CH=N- o un grupo -C=C-;

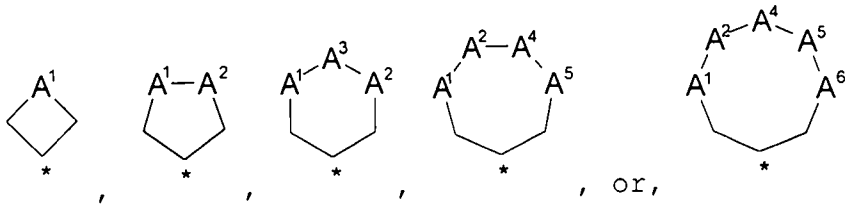
e) Z^1 se elige de H, CH_3 o $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14}, $COOR^{14}$ o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede sustituirse con un alquilo inferior;

f) A es un ciclo seleccionado de:



, , , , or,

en donde

- A^1, A^2, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,
  - alquilo no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} and R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- A^3 se selecciona de O, S, C, C(=O), SO o SO_2, o N-R^{18} cuando A^1 y/o A^2 son C(=O) o cuando Y es O o S, en donde R^{18} es lo definido anteriormente;

- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;
- 2 átomos del ciclo A, qu no son adyacentes, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que:

- no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;

- el ciclo A no contenga más de dos átomos de carbono en un estado de hibridación de sp^2;
- cuando X es O, X_2 no sea C-R^1 en donde R^1 es
  - un tienilo sustituido con CN o con CN y CH_3,
  - un fenilo sustituido con CN, Cl, NO_2 o CN y F,
  - Br
  - F;

o sus formas tautoméricas, sus formas racémicas o sus isómeros y sus derivados farmacéuticamente aceptables.

Estos compuestos son inhibidores selectivos de PDE7. Pueden usarse en el tratamiento de diversas enfermedades, tales como enfermedades relacionadas con las células T, enfermedades autoinmunes, osteoartritis, artritis reumatoide, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirido (SIDA), alergia o enfermedad intestinal inflamatoria (IBD).

La invención también se relaciona con un proceso para preparar los compuestos precedentes.

La invención además se refiere al uso de un compuesto de la fórmula (I), (II) o (III) para la preparación de un medicamento para la prevención o el tratamiento de trastornos

para los cuales la terapia con un inhibidor de PDE7 es relevante.

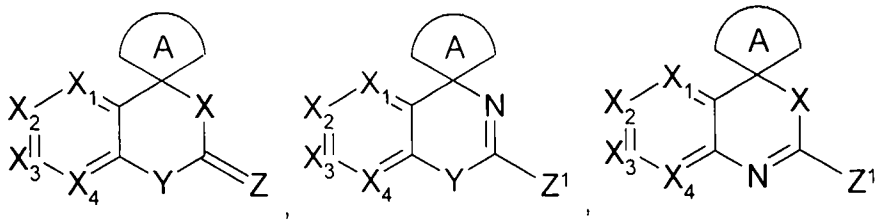
La invención también proporciona un método para el tratamiento de un trastorno para el cual la terapia con un inhibidor de PDE7 es relevante, que comprende administrar a un mamífero que lo necesita una cantidad efectiva de un compuesto de la fórmula (I), (II) o (III).

La invención también provee un método para el tratamiento de enfermedades relacionadas con las células T, enfermedades autoinmunes, osteoartritis, artritis reumatoide, esclerosis múltiple, enfermedad pulmonar obstructiva crónica (COPD), asma, cáncer, síndrome de inmunodeficiencia adquirido (SIDA), alergia o enfermedad intestinal inflamatoria (IBD), que comprende administrar a un mamífero que lo necesita una cantidad efectiva de un compuesto de la fórmula (I), (II) o (III).

La invención también se refiere a una composición farmacéutica que comprende un compuesto de la fórmula (I), (II) o (III) junto con un portador, excipiente, diluyente o sistema de administración farmacéuticamente aceptable.

Descripción Detallada de la Invención

La invención presente proporciona el uso de compuestos, que son inhibidores de PDE, que tienen las fórmulas (I), (II) o (III):



(I) (II) (III)

en donde:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

-C-R^1, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,
    - alquilo inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de

estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o $=N-R^6$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

- R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
- hidrógeno,

- alquilo inferior optativamente interrumpido con C(=O), $(CH_2)_n$-arilo, $(CH_2)_n$-heteroarilo, $(CH_2)_n$-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o $(CH_2)_n$-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde n es un número entero seleccionado de 0, 1, 2, 3 o 4;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, SO_3H, CH_3, SO_2CH_3, CF_3, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

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- un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de

- H o

- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o

b) X es O, S o NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos compuestos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10} o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10} o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de $CH-NO_2$, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14} o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, puden formar un anillo heterocíclico de 4

a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior o

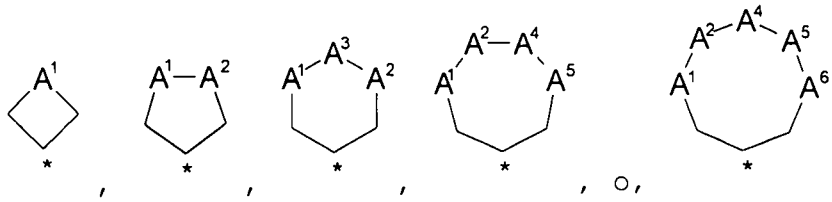
e) Z^1 se elige de H, CH_3 o $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14} o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o más heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior;

f) A es un ciclo elegido de:



, , , , o,

en donde

- A^1, A^2, A^3, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,
  - alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo

inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

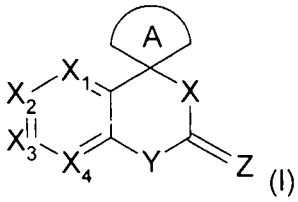
- 2 átomos del ciclo A, que no son adyacente, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;

o sus formas tautoméricas, sus formas racémicas o sus isómeros y sus derivados farmacéuticamente aceptables,

para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

Un uso preferido se refiere a los inhibidores de PDE7 de la fórmula (I)



(I)

en donde X_1, X_2, X_3, X_4, X, Y, Z y A son lo definido anteriormente,

para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

Un uso más preferido se refiere a los inhibidores de PDE7 de la fórmula (II) o (III) en donde:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3

grupos seleccionados de halógeno, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde

- X^5 se selecciona de alquileno inferior o un solo enlace y

- R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH-C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:

  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y

  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo

heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N, y pueden ser sustituidos con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y,

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos selecciondos de O, S o N;

b) X_4 es C-R^1 en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

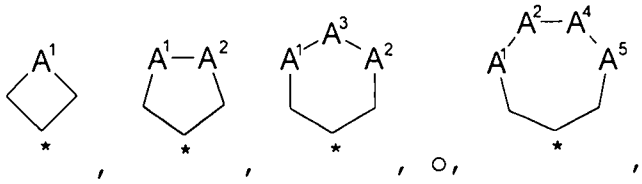
e) Z^1 se elige de $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14} o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior, y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N, y que pueden ser sustituidos con un alquilo inferior;

f) A es un ciclo elegido de:



en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:
  - un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes ,seleccionados de alquilo inferior, OH o F, o,
  - un átomo oxígeno;
- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;

- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono,

siempre que:

- no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representa un átomo de oxígeno;

para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

Un uso particularmente preferido se refiere a los inhibidores de PDE7 de la fórmula (I) en donde:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, OR^2, $COOR^2$, NR^3R^4,

$SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde
  - X^5 se selecciona de alquileno inferior o un solo enlace y
  - R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, NH-$C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno

o dos heteroátomos seleccionados de O, S o N, y pueden ser sustituidos con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y,

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos selecciondos de O, S o N;

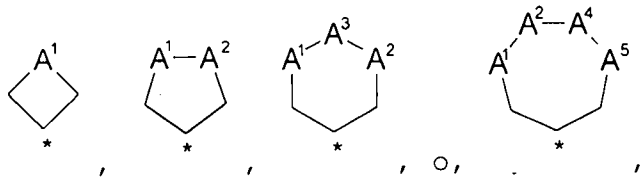
b) X_4 es C-R^1 en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

e) Z^1 se elige de O, S o NR^{13} en donde R^{13} es hidrógeno o CN;

f) A es un ciclo elegido de:



en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:
  - un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes ,seleccionados de alquilo inferior, OH o F, o,
  - un átomo oxígeno;
- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono,

siempre que:

- no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representa un átomo de oxígeno;

para la prevención o el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

Un grupo preferido de compuestos de la fórmula (II) o (III) son aquellos en donde:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde

  - X^5 se selecciona de alquileno inferior o un solo enlace y

  - R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH-C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N, y pueden ser sustituidos con
    - un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
    - un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de

- H, o,
- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y,

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos selecciondos de O, S o N;

b) X_4 es $C-R^1$ en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

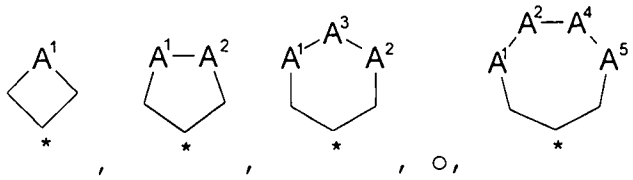
e) Z^1 se elige de $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14} o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior, y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N, y que pueden ser sustituidos con un alquilo inferior;

f) A es un ciclo elegido de:



, , , o, ,

en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:
  - un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes ,seleccionados de alquilo inferior, OH o F, o,
  - un átomo oxígeno;
- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono,

siempre que:

- no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representa un átomo de oxígeno.

Un grupo preferido de compuesto de la fórmula (II) o (III) son aquel en donde X_1, X_2, X_3, X_4, X, Y, Z_1 y A son los revelados anteriormente en donde cuando X_2 es $C-R^1$ y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Otro grupo preferido son los compuestos de la fórmula (I) en donde:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

$-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,
    - alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o $=N-R^6$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y
  - R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o

con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, $Q\text{-}R^2$, $Q\text{-}NR^3R^4$, $NR^2\text{-}Q\text{-}NR^3R^4$ o $NR^3\text{-}Q\text{-}R^2$ en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
- hidrógeno,
- alquilo inferior optativamente interrumpido con C(=O), $(CH_2)_n$-arilo, $(CH_2)_n$-heteroarilo, $(CH_2)_n$-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o $(CH_2)_n$-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde n es un número entero seleccionado de 0, 1, 2, o 3;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, SO_3H, CH_3, SO_2CH_3, CF_3, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

  - un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

  - un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de

  - H o

  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8

miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o

b) X es NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos compuestos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10} o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10} o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o

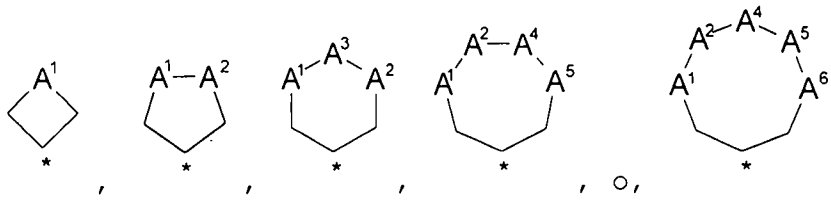
diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de $CH-NO_2$, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14} o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, puden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior;

e) A es un ciclo elegido de:



, , , , o,

en donde

- A^1, A^2, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,
  - alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
  - A^3 se selecciona de O, S, C, C(=O), SO o SO_2 o N-R^{18} cuando A^1 y/o A^2 son C(=O) o cuando Y es O o S, en donde R^{18} es lo definido anteriormente;

- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, selecccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;
- 2 átomos del ciclo A, que no son adyacentes, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que:

- no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;

- el ciclo A no contenga más de 2 átomos de carbono en un estado de hibridación de sp^2.

Un grupo preferido de compuestos de la fórmula (I) es un grupo en el cual X_1, X_2, X_3, X_4, X, Y, Z y A son lo revelado anteriormente en donde cuando X_2 es $C-R^1$ y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Los compuestos preferidos de la fórmula (I) son aquellos en donde:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

$-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,
    - alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, o N, los átomos de carbono de estos

grupos son no sustituidos o sustituidos con 1 o 2 grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o =N-R^6 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

- R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, o N, o un grupo bicíclico,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, $Q\text{-}R^2$, $Q\text{-}NR^3R^4$, $NR^2\text{-}Q\text{-}NR^3R^4$ o $NR^3\text{-}Q\text{-}R^2$ en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
- hidrógeno,
- alquilo inferior optativamente interrumpido con C(=O), $(CH_2)_n$-arilo, $(CH_2)_n$-heteroarilo, $(CH_2)_n$-

cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o $(CH_2)_n$-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde n es un número entero seleccionado de 0, 1, 2, o 3;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, SO_3H, CH_3, SO_2CH_3, CF_3, OR^6, $COOR^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

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- un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de
- H o
- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

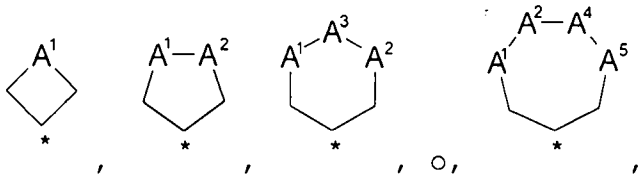
R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o

b) X es NH;

c) Y es NH;

d) Z se elige de O, S o NR^{13} en donde R^{13} es hidrógeno o CN;

e) A es un ciclo elegido de:



, , , o, ,

en donde

- A^1, A^2, A^4 y A^5 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,

cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,

- alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- A^3 se selecciona de O, S, C, C(=O), SO o SO_2 o $N-R^{18}$ cuando A^1 y/o A^2 son C(=O) o cuando Y es O o S, en donde R^{18} es lo definido anteriormente;
- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos

o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- 2 átomos del ciclo A, que no son adyacentes, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que:

- no más de dos de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representen un heteroátomo;
- el ciclo A no contenga más de 2 átomos de carbono en un estado de hibridación de sp^2.

Un grupo preferido de los compuestos de la fórmula (I) es un grupo en donde X_1, X_2, X_3, X_4, X, Y, Z y A son lo revelado anteriormente en donde cuando X_2 es C-R^1 y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Compuestos más preferidos de la fórmula (I) son aquellos en donde:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde

  -X^5 se selecciona de un alquileno inferior o un solo enlace

  y

  -R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N, y puede ser sustituido con
    - un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o
    - un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de

- H, o,
- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembors, que puede contener uno o dos heteroátomos seleccionados de O, S o N;

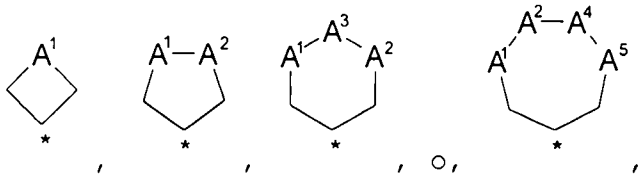
b) X_4 es C-R^1 en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ o $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

e) Z se elige de O, S o NR^{13} en donde R^{13} es hidrógeno o CN;

f) A es un ciclo elegido de:



, , , o, ,

en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:

- un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior, OH o F, o,
- un átomo de oxígeno;

- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono;

siempre que:

no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representen un átomo de oxígeno.

Un grupo preferido de compuestos de la fórmula (I) es un grupo en el cual X_1, X_2, X_3, X_4, X, Y, Z y A son lo revelado anteriormente en donde cuando X_2 es $C-R^1$ y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Los compuestos más preferidos de la fórmula (I) son aquellos en donde:

a) X_1, X_2 y X_3 son iguales o diferentes y son $C-R^1$, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, OR^2, en donde R^2 se selecciona de hidrógeno o alquilo inferior;

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

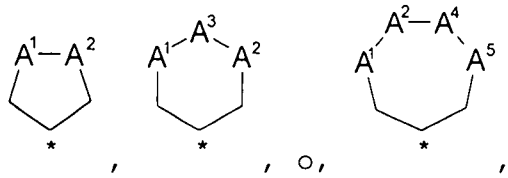
b) X_4 es $C-R^1$ en donde R^1 se selecciona de hidrógeno, halógeno, CH_3, CN, OR^2, en donde R^2 se selecciona de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

e) Z se elige de O, S o NR^{13} en donde R^{13} es hidrógeno o CN;

f) A es un ciclo elegido de:



, , o, ,

en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de átomos de carbono, no sustituidos o sustituidos con CH_3;

- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono.

Preferentemente, X_1, X_2, X_3 y X_4 son iguales o diferentes y son $C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos Q_2;
- el grupo X^5-R^5 en donde
  - X^5 se selecciona de:
    - un solo anillo,
    - un alquileno inferior, optativamente interrumpido con 1 heteroátomo elegido de O, S y N
  - R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico

estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR' o NR'R''

en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

- n es un número entero seleccionado de 0, 1, 2, 3 o 4;

- estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

  - $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o

- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N.

Un grupo preferido de compuestos de la fórmula (I) es un grupo en el cual X_1, X_2, X_3 y X_4, son lo revelado anteriormente en donde cuando X_2 es C-R^1 y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Preferentemente, X_1, X_2, X_3 y X_4 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 átomos de flúor, OR^3, $COOR^3$ o NR^3R^4 en donde R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, pueden formar también un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N;

- el grupo X^5-R^5 en donde X^5 es un solo enlace y R^5 se selecciona de arilo, preferentemente fenilo, heteroarilo, preferentemente piridilo, o un grupo bicíclico, preferentemente indolilo, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3,

en donde Q_1 y Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, alquilo inferior,
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ o $SO_2NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior, $(CH_2)_n$-heteroarilo en donde n es un número entero seleccionado de 0, 1, 2 o 3;
    estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de CN, SO_3H, OR^6, $COOR^6$ o NR^6R^7, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior, y

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- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 6 miembros que puede contener uno o dos heteroátomos seleccionados de O o N, y que puede ser sustituido con

- un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N y que puede ser sustituido con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o,
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'', junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N.

Un grupo preferido de compuestos de la fórmula (I) es un grupo en donde X_1, X_2, X_3 y X_4, son lo revelado anteriormente en donde cuando X_2 es C-R^1 y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Un grupo preferido de compuestos es el grupo en donde uno de X_1, X_2, X_3 y X_4 es C-R^1 en donde R^1 es hidrógeno mientras los

demás son idénticos o diferentes y son C-R^1 en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos Q_2;
- el grupo X^5-R^5 en donde
  - X^5 se selecciona de:
    - un solo enlace,
    - un alquileno inferior, optativamente interrumpido con 1 heteroátomo elegido de O, S y N
  - R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico,

    estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H,

- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, aluenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR' o NR'R'' en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;
    - n es un número entero seleccionado de 0, 1, 2, 3 o 4;
  - estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en

donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior, y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con
  - $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior, o
  - un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, puede formar un anillo heterocíclico de 4 a 8 miembros, que

puede contener uno o dos heteroátomos seleccionados de O, S o N.

Un grupo preferido de compuestos de la fórmula (I) es un grupo en el cual X_1, X_2, X_3 y X_4, son lo revelado anteriormente en donde cuando X_2 es $C-R^1$ y R^1 es X^5-R^5, entonces X^5 no es un solo enlace.

Un grupo preferido de compuestos es el grupo en el cual uno de X_1, X_2, X_3 y X_4 es $C-R^1$ en donde R^1 es hidrógeno mientras que los demás son idénticos o diferentes y son $C-R^1$ en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos halógeno o con OR^3, $COOR^3$ o NR^3R^4 en donde R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

  R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, pueden formar también un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N;
- el grupo X^5-R^5 en donde X^5 es un solo enlace y R^5 se selecciona de arilo, preferentemente fenilo, heteroarilo, preferentemente piridilo, o un grupo bicíclico,

preferentemente indolilo, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3,

en donde Q_1 y Q_3 son iguales o diferentes y se seleccionan de

- halógeno, CN, alquilo inferior
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ o $SO_2NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior, $(CH_2)_n$-heteroarilo en donde n es un número entero seleccionado de 0, 1, 2 o 3;
    estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de CN, SO_3H, OR^6, $COOR^6$ o NR^6R^7, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N, y que puede ser sustituido con
- un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N y que puede ser sustituido con un alquilo inferior, o

- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o,
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N.

Un grupo preferido de compuesto es el grupo revelado anteriormente en donde X^3 es C-R^1 en donde R^1 es hidrógeno.

Preferentemente, X_3 es C-R^1, en donde R^1 se selecciona de:

- hidrógeno o halógeno, preferentemente Cl, o,
- X^5-R^5 en donde R^5 es solo enlace y R^5 es arilo, preferentemente fenilo o heteroarilo, preferentemente piridilo, optativamente sustituido con uno, dos o tres grupos que son iguales o diferentes y que se seleccionan de halógeno, CN, CF_3, SO_2Me, OR^2, $COOR^2$, NR^2R^3, $SO_2NR^2R^3$ y $CONR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno y alquilo inferior.

Preferentemente, X_3 es C-R^1, en donde R^1 se selecciona de hidrógeno o halógeno, preferentemente Cl.

Preferentemente, X_3 es C-R^1 en donde R^1 es hidrógeno.

Preferentemente, X_4 es C-R^1, en donde R^1 se selecciona de

- hidrógeno, halógeno, CF_3, O-alquilo inferior, $COOR^2$ o,
- alqilo inferior optativamente sustituido con OR^2, $COOR^2$ o $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior.

Preferentemente, X_4 es C-R^1, en donde R^1 se selecciona de hidrógeno, halógeno, CF_3, metilo y metoxi.

Preferentemente, X_1 es C-R^1, en donde R^1 se selecciona de

- hidrógeno, halógeno, preferentemente Cl o Br, OR^2, COR^2, $COOR^2$,$CONR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de
  - hidrógeno,
  - alquilo inferior, Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, or N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior;
    - n es un número entero seleccionado de 0, 1, 2 o 3;

estos grupos son no sustituidos o sustituidos con CN, OR^6, SO_3H, $CONR^6R^7$, $COOR^6$, COR^6 o NR^6R^7,

en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, optativamente sustituido con NH_2, COOH, OH;

R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con

- $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o
- COR' o alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se selecccionan de hidrógeno o alquilo inferior;

- alquilo inferior optativamente sustituido con CN, SO_3H, OR^3, NR^3R^4, $COOR^3$ o $CONR^3R^4$ en donde R^3 y R^4 son iguales o diferentes y se seleccionan de
  - hidrógeno y
  - alquilo inferior optativamente sustituido con OH, COOH o NH_2

- el grupo X^5-R^5 en donde X^5 es un alquileno inferior optativamente interrumpido con un heteroátomo seleccionado de O y N y R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S o N y cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S o N,

estos grupos son no sustituidos o sustituidos con OR^3 o $COOR^3$ en donde R^3 se selecciona de hidrógeno y alquilo;

R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N, y que puede ser sustituido con

- $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con alquilo inferior o
- C(=O)-R' o un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior.

Preferentemente, X_1 es C-R^1, en donde R^1 se selecciona de hidrógeno, halógeno, preferentemente Cl o Br, o OR^2 en donde R^2 se selecciona de

- hidrógeno,
- alquilo inferior, no sustituido o sustituido con CN, OR^6, SO_3H, $COOR^6$ o NR^6R^7,
- $(CH_2)_n$-oxadiazol, $(CH_2)_n$-tetrazol , $(CH_2)_n$-morfolina, $(CH_2)_n$-furano, no sustituido o sustituido con OR^6 o $COOR^6$,

en donde n es 1 o 2 y R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, optativamente sustituido con NH_2 o COOH.

Preferentemente, X_2 es C-R^1, en donde R^1 es X^5-R^5, en donde

-X^5 es un solo enlace,

-R^5 es fenilo o piridilo,

- optativamente sustituido con alquilo inferior, y
- sustituido con $C(=O)NR^3R^4$ en donde R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con
- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N que puede ser sustituido con un alquilo inferior o

- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o,
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados seleccoinados de O, S or N.

Preferentemente, X_2 es C-R^1, en donde R^1 es X^5-R^5, en donde

-X^5 es un solo enlace

-R^5 es fenilo,

- optativamente sustituido con un metilo, y
- subtituido con C(=O)NR^3R^4 en donde R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 6 miembros, que puede contener uno o dos átomos de nitrógeno y que puede ser sustituido con

- un anillo heterocíclico de 6 miembros, que puede contener uno o dos átomos de nitrógeno y que puede ser sustituido con un alquilo inferior o

- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
    - H, o,
    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

  R' y R'' junto con el átomo de nitrógeno al cual están unidos puden formar un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N.

En cada uno de todos los grupos de compuestos definidos anteriormente, las siguientes sustituciones son preferidas.

Preferentemente, los compuestos de la invención son compuestos de la fórmula (I).

Preferentemente, X es NH.

Preferentemente, Y es NH.

Preferentemente, Z es O.

Preferentemente, X es NH, Y es NH, y Z es O.

Preferentemente, A se selecciona de ciclohexilo o cicloheptilo, optativamente interrumpido con C(=O) o O, y no sustituido o sustituido con CH_3, OH o OCH_3.

Preferentemente, A se selecciona de ciclohexilo o cicloheptilo no sustituido.

Preferentemente, A es ciclohexilo no sustituido.

Preferentemente X es NH, Y es NH, Z es O y A es ciclohexilo no sustituido.

Preferentemente X es NH, Y es NH, Z es O, A es ciclohexilo no sustituido, X_3 es C-R^1 en donde R^1 es hidrógeno y X_4 es C-R^1, en donde R^1 se selecciona de hidrógeno, halógeno, CF_3, metilo o metoxi.

En el siguiente y en texto precedente:

Halógeno incluye fluoro, cloro, bromo, y yodo. Los halógenos preferidos son F y Cl.

Alquilo inferior incluye cadenas de carbono rectas y ramificadas que tienen de 1 a 6 átomos de carbono. Ejemplos de tales grupos alquilo incluyen metilo, etilo, isopropilo, terc-butilo y similares.

Alquenilo incluye radicales hidrocarburo rectos y ramificados que tienen de 2 a 6 átomos de carbono y por lo menos un doble enlace. Ejemplos de tales grupos son etenilo, 3-buten-1-ilo, 2-etenilbutilo, 3-hexen-1-ilo, y similares.

Alquinilo inferior incluye radicales hidrocarburo rectos y ramificados que tienen de 2 a 6 átomos de carbono y por lo menos un enlace triple. Ejemplos de tales grupos alquinilo son etinilo, 3-butin-1-ilo, propinilo, 2-butin-1-ilo, 3-pentin-1-ilo, y similares.

Haloalquilo inferior incluye un alquilo inferior definido anteriormente, sustituido con uno o varios halógenos. Un haloalquilo preferido es trifluorometilo.

Por arilo se entiende un carbociclo aromático que contiene entre 6 y 10, preferentemente 6, átomos de carbono. Un grupo arilo preferido es fenilo.

Heteroarilo includye ciclos aromáticos que tienen de 5 a 10 átomos del anillo, de 1 a 4 de los cuales se seleccionan independientemente del grupo formado por O, S, y N. Los grupos heteroarilo peferidos tienen 1, 2, 3 o 4 heteroátomos en un anillo aromático de 5 o 6 miembros. Ejemplos de tales grupos son tetrazol, piridilo, tienilo y similares.

Los cicloalquilo preferidos contienen de 3 a 8 átomos de carbono. Ejemplos de tales grupos son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo u ciclooctilo.

El término "interrumpido" significa que en una cadena principal, un átomo de carbono es reemplazado por un heteroátomo o un grupo definido anteriormente. Por ejemplo, en "cicloalquilo o cicloalquenilo optativamente interrumpido con C(=O) o con 1 heteroátomo elegido de O, S, S(=O), SO_2 o N", el término "interrumpido" significa que C(=O) o un heteroátomo puede reemplazar a un átomo de carbono del anillo. Ejemplos de tales grupos son morfolina y piperazina.

Cicloalquenilo incluye cicloalquenilo de 3 a 10 miembros que contiene por lo menos un enlace doble.

Anillos heterocíclicos incluyen heteroarilo definido anteriormente y cicloalquilo o cicloalquenilo, definido anteriormente, interrumpido con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2, o N.

Sustituyentes bicíclicos se refieren a dos ciclos, que son iguales o diferentes y que se eligen de arilo, anillo heterocíclico, cicloalquilo o cicloalquenilo, fusionados juntos para formar dichos sustituyentes bicíclicos. Un sustituyente bicíclico preferido es indolilo.

Estado de hibridación Sp^2: los átomos de carbono en estado de hibridación sp^2 son trigonales en lugar de tetrahédricos. Esto

significa que los átomos de carbono en estado de hibridación sp^2 están unidos a tres átomos y forman un enlace doble con uno de estos tres átomos.

Los compuestos preferidos son:

Espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

Espiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

7'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-Fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

7'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-choroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-fluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6',7'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',6'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[ciclobutano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromo-4-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-onae,

8'-Bromoespiro[biciclo[3,2,1]octano-2-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

8'-cloro-6'-yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(1H-indol-5il)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(2-N-dimetilamino-etilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro -6'-[3-(4-metil-piperazin-1-carbonil)-fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(2-N-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-tiona

8'-Cloro-2'-cianoiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina

8'-Cloro-2'-metoxiiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina,

8'-Cloro-2'-dimetilaminoespiro[ciclohexane-1-4'-(3',4'-dihidro)quinazolina],

8'-Cloro-1'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-1'-(etoxicarbonilmetil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-Cloro-3'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazina-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-imidazo[2,1-b]quinazolina

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-[1,2,4]triazolo[3,4-b]quinazolina,

9'-Cloroespiro[ciclohexane-1-5'-(4',5'-dihidro)]-[1,2,4]triazolo[4,3-a]quinazolina,

Espiro[ciclohexano-1-9'-(8',9'-dihidro)-pirazolo[4',3'-f]quinazolin]-7'(6'H)-ona,

8'-Cloro-5'-metoxiespiro[ciclohexane-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-difluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-(morfolin-4-il)metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxi-6'-yodo-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-yodo-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-dimetilaminoetoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-aminoetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(metilamino)etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(2-aminoetoxi)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[3-dimetilaminopropoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-etoxicarbonilmetoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboximetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxipropoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-(3-sulfopropoxi)-espiro[ciclohexaoe-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(tetrahidro-piran-2-iloxi)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-etoxicarbonil-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-yodo-5'-[2-dimetilamino-etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

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8'-cloro-6'-[2-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-metoxi-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8-Cloro-5-metoxiespiro[4H-benzo[d][1,3]oxazin-2-ilamino-4-4'-(tetrahidro-piran-4'-ilo)],

8'-Trifluorometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-cianometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-dimetilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-metilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(etoxicarbonilmetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona.

Entre los compuestos mencionados anteriormente, los siguientes compuestos son más preferidos:

6'-Fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-fluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',6'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromo-4-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[biciclo[3,2,1]octano-2-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

8'-cloro-6'-yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(1H-indol-5il)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(2-N-dimetilamino-etilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro -6'-[3-(4-metil-piperazin-1-carbonil)-fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(2-N-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-tiona

8'-Cloro-2'-cianoiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina

8'-cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-difluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-(morfolin-4-il)metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-dimetilaminoetoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(metilamino)etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboximetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxipropoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-(3-sulfopropoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-etoxicarbonil-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-metoxi-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-cianometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-dimetilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-metilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona.

Entre los compuestos mencionados anteriormente, los siguientes compuestos son más preferidos:

8'-bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(1H-indol-5il)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(2-N-dimetilamino-etilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro -6'-[3-(4-metil-piperazin-1-carbonil)-fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(2-N-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboximetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxipropoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-(3-sulfopropoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-ehoxicarbonil-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexaoe-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

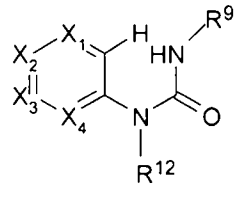
8'-cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil] espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona, y

clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona.

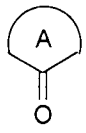
Proceso General para la preparación de los compuestos de la invención

Un método para preparar un compuesto de la fórmula (I) definido anteriormente en el cual Y es N-R^{12}, X es N-R^9 y Z es O, comprende la reacción de una urea sustituida de la fórmula



,

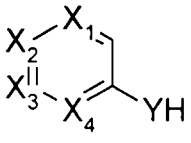
en donde X_1, X_2, X_3, X_4, R_9 y R_{12} son lo definido en el resumen de la invención, con una cetona cíclica de la fórmula



en donde A es lo definido en el resumen de la invención, para obtener el compuesto de la fórmula (I) mencionado.

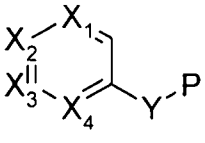
Un método alternativo para perparar un compuesto de la fórmula (I) en donde X es N-R^9, Y es O, S o NH, y X_1, X_2, X_3, X_4, A y R^9 son lo definido en el resumen de la invención, comprende

(1) reaccionar un compuesto (2a)



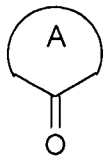
(2a)

en donde X_1, X_2, X_3, X_4 son lo definido en el resumen de la invención e Y es O, S o NH, con un grupo P-LG en donde P es un grupo protector y LG es un grupo saliente para obtener un compuesto (2b)

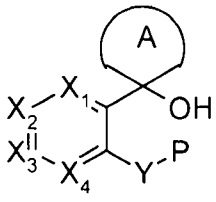


(2b)

(2) reaccionar el compuesto (2b) con R-Li en donde R es alquilo inferior y luego con una cetona de la fórmula

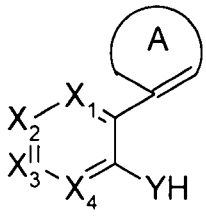


en donde A es lo definido en el resumen de la invención para obtener el compuesto (2c)



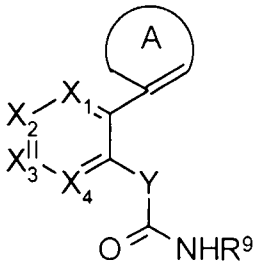
(2c)

(3) remover el grupo protector P en condiciones reductoras, en condiciones ácidas o en condiciones básicas para obtener el compuesto (2d)



(2d)

(4) reaccionar el compuesto (2d) con un grupo $O=C=N-R^9$ en donde R^9 es lo definido en el resumen de la invención para obtener el compuesto (2e)



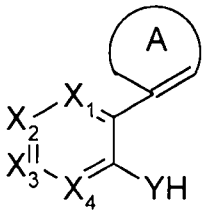
(2e)

(5) reaccionar el compuesto (2e) con un ácido para obtener el compuesto de la fórmula (I) mencionado,

(6) aislar dicho compuesto de la fórmula (I).

Un proceso alternativo para la preparación de un compuesto de la fórmula (I) en donde X es O, S o NR^9, Y es O, S o NR^{12}, Z es O, S o NR^{13}, X_1, X_2, X_3, X_4, A, R^9, R^{12} y R^{13} son lo definido en el resumen de la invención e Y es O, S o NH, comprende

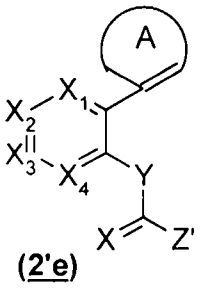
(1) reaccionar el compuesto (2d)



(2d)

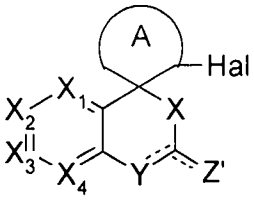
en donde X_1, X_2, X_3, X_4 y A son lo definido en la reivindicación 1,

con un grupo LG-C(=X)Z' o X=C=Z' en donde LG es un grupo saliente, X es O, S o NR^9, Z' es OR, SR o NR^{13} en donde R es alquilo inferior o bencilo R^9 y R^{13} son lo definido en el resumen de la invención, para obtener el compuesto (2'e)



(2'e)

(2) reaccionar el compuesto (2'e) con una fuente de halonio para obtener el compuesto (2'f)



(2'f)

(3) reducción del compuesto (2'f) para obtener dicho compuesto de la fórmula (I)

(4) optativamente, cuando Z' es OR o SR, la hidrólisis o hidrogenólisis del compuesto (2'f) se lleva a cabo para obtener dicho compuesto de la fórmula (I) en donde Z es O o S, y

(5) aislar dicho compuesto de la fórmula (I).

Los compuestos utilizados en la invención incluyen derivados farmacéuticamente aceptables de compuestos de la fórmula (I), (II) o (III) tales como solvatos, hidratos, sales farmacéuticamente y polimorfos (descriptores reticulados cristalinos diferentes).

Las sales farmacéuticamente aceptables de un compuesto de la fórmula (I), (II) o (III) incluyen sales que tienen una parte básica y sales que tienen una parte ácida.

Por la expresión sal farmacéuticamente aceptable de un compuesto de la fórmula (I), (II) o (III) que tiene una parte básica debe entenderse las sales de adición de los compuestos de la fórmula (I), (II) o (III) que pueden formarse a partir de ácidos inorgánicos u orgánicos no tóxicos tales como, por ejemplo, sales del ácido bromhídrico, clorhídrico, sulfúrico, fosfórico, nítrico, acético, succínico, tartárico, cítrico, maleico, hidroximaleico, benzoico, fumárico y toluenosulfónico y similares. Las diversas sales de amonio cuaternario de los derivados (I), (II) o (III) también están incluidas en esta categoría de compuestos de la invención. Además, por la expresión sal farmacéuticamente acceptable de un compuesto de la fórmula (I), (II) o (III) que tiene una parte ácida, se entiende las sales habituales de los compuestos de la fórmula (I), (II) o (III) que pueden formarse desde las bases inorgánicas u orgánicas no tóxicas tales como, por ejemplo, los hidróxidos de metales alcalinos y de metales alcalinotérreos (sodio, potasio, magnesio y calcio), aminas (dibenciletilendiamina, trimetilamina, piperidina, pirrolidina, bencilamina y similares) o alternativamente hidróxidos de amonio cuaternario tales como hidróxido de tetrametilamonio. (Ver

también "Sales farmacéuticas" por Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, que se incorpora en la presente invención como referencia.)

También está contemplado el uso de una prodroga de un compuesto de la invención tal como se le ocurriría a un experto en el arte (ver Bundgaard, *et al.*, Acta Pharm. Suec., 1987; **24**: 233-246).

Composiciones farmacéuticas

Los productos de la invención se administran en la forma de composiciones, que son apropiadas para la naturaleza y la gravedad de la enfermedad que se ha de tratar. La dosis diaria en humanos es generalmente entre 1 mg y 1 g del producto, que se puede tomar en una o más dosis individuales. Las composiciones se preparan en formas que son compatibles con la vía de administración deseada, tal como por ejemplo, tabletas, tabletas recubiertas, cápsulas, enjuagues bucales, aerosoles, polvos para inhalación, supositorios, enemas, espumas (tales como espumas rectales), geles o suspensiones. Estas composiciones se preparan mediante métodos que son familiares para los expertos en el arte y comprenden del 0,5% al 60% en peso del principio activo (el compuesto de la invención) y del 40% al 99,5% en peso de un vehículo o portador farmacéutico

que es apropiado y compatible con el principio activo y la forma física de la composición deseada.

Las preparaciones en forma sólida incluyen polvos, tabletas, gránulos dispersables, cápsulas, y supositorios. Un portador sólido puede ser una o más sustancias que también pueden actuar como diluyentes, agentes saborizantes, solubilizadores, lubricantes, agentes de suspensión, ligantes, o agentes desintegradores de las tabletas; también puede ser un material encapsulante. En los polvos, el portador es un sólido finamente dividido, que se mezcla con el componente activo finamente dividido. En las tabletas, el componente activo se mezcla con el portador que tiene las propiedades ligantes necesarias en proporciones adecuadas y se compacta en la forma y tamaño deseados. Los polvos, tabletas, cápsulas o formas encapsuladas para cápsulas preferentemente contienen del 5% al 70% del componente activo. Los portadores adecuados son carbonato de magnesio, estearato de magnesio, talco, lactosa, azúcar, pectina, dextrina, almidón, tragacanto, metil celulosa, carboximetil celulosa de sodio, una cera de bajo punto de fusión, manteca de cacao y similares.

Las tabletas, polvos y cápsulas pueden usarse como formas de dosificación sólidas para la administración oral. La droga se puede administrar como una aspersión (en un recipiente

presurizado equipado con una válvula apropiada o en un recipiente no presurizado equipado con una válvula medidora).

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones.

Las soluciones estériles en agua o agua-propilenglicol de los compuestos activos pueden mencionarse como un ejemplo de preparaciones líquidas adecuadas para la administración parenteral. Las preparaciones líquidas también pueden formularse en solución en polietilenglicol acuoso.

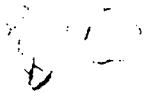
Las soluciones acuosas para la administración oral pueden prepararse disolviendo el componente activo en agua y agregando colorantes, agentes saborizantes, estabilizadores, y agentes espesantes adecuados según se desee. Las suspensiones acuosas para uso oral pueden fabricarse dispersando el componente activo finamente dividido en agua junto con u aterial viscoso tal como gomas naturales, sintéticas, resinas, metil celulosa, carboximetil celulosa de sodio, y otros agentes de suspensión conocidos para el arte de las formulaciones farmacéuticas.

Para preparar preparaciones en supositorios, una cera de bajo punto de fusión tal como una mezcla de gicéridos de ácidos

grasos y manteca de cacao se funde primero y el ingrediente activo se dispersa en ella, por ejemplo, mediante agitación. La mezcla homogénea fundida se vierte luego en moldes de dimensiones convenientes y se deja enfriar y solidificar. Los enemas se obtienen de acuerdo con procedimientos conocidos para perparar soluciones para la administración rectal. Las espumas se preparan de acuerdo con métodos conocidos (estas espumas pueden ser notablemente similares a aquellas usadas para administrar una droga tal como la 5-ASA para tratar rectocolito).



Preferentemente, la preparación farmacéutica está en forma de dosificación unitaria. En tal forma, la preparación se divide en dosis unitarias que contienen cantidades apropiadas de la droga. La forma de dosificación unitaria puede ser una preparación empaquetada, el paquete contiene cantidades discretas de la preparación, por ejemplo, tabletas empaquetadas, cápsulas y polvos en frascos o ampollas. La forma de dosificación unitaria también puede ser una cápsula o la propia tableta, o puede ser el número apropiado de cualquiera de estas formas empaquetadas.



Métodos de Tratamiento

Los compuestos de la invención son inhibidores de PDE, y particularmente inhibidores de PDE7. Estos compuestos tienen bajos valores de IC_{50}, típicamente como máximo 5 µM, preferentemente inferiores a 1 µM, y aún inferiores a 100 nM.

Se ha mosrtado de acuerdo con la invención que los compuestos de la invención son inhibidores selectivos de PDE7. "Inhibidores selectivos de PDE7" se refiere a compuestos que tienen un IC_{50} para PDE7 por lo menos 5 veces inferior al IC_{50} para una PDE distinta de PDE7, y preferentemente por lo menos 10 veces, 15 veces, 20 veces, 30 veces, 40 veces, 50 veces o 100 veces menor que el IC_{50} para una PDE distinta de PDE7.

Una PDE distinta de PDE7 se refiere preferentemente a una PDE elegida de PDE1, PDE3, PDE4 o PED5.

En particular, se ha demostrado de acuerdo con la invención que los compuestos de la invención, y más particularmente la familia de los compuestos dados como ejemplos en la presente invención, tienen un valor de IC_{50} para la enzima PDE7 que es frecuentemente 100 inferior al valor de sus IC_{50} para una PDE distinta de PDE7, en particular PDE1, PDE3, PDE4 o PDE5.

Los compuestos de la invención pueden usarse en el tratamiento de diversas enfermedades, ya que modulan procesos inflamatorios

e inmunológicos debido al incremento de los niveles intracelulares de cAMP.

Las enfermedades que pueden tratarse son enfermedades relacionadas con las células T, enfermedades relacionadas con las células AE y trastornos inmunes, tales como enfermedades autoinmunes, osteoartritis, artritis reumatoide, esclerosis múltiple, asma, COPD, cáncer, SIDA, inflamación, alergia y diversos trastornos inflamatorios tales como, por ejemplo, enfermedad intestinal inflamatoria (IBD).

La invención finalmente se relaciona con un método para el tratamiento de las enfermedades mencionadas anteriormente que comprende administrar a un mamífero, particularmente un humano, que lo necesita una cantidad efectiva del compuesto de la invención.

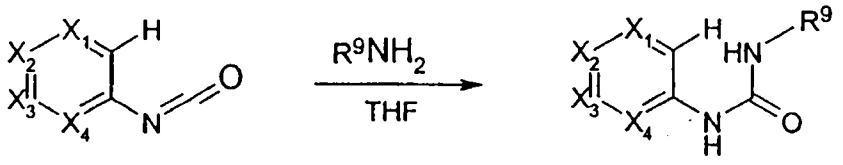
Procesos para sintetizar los compuestos de la fórmula general (I), (II) y (III)

Los compuestos de acuerdo con la presente invención pueden obtenerse llevando a cabo varios procesos sintéticos. Algunos de estos procesos sintéticos (protocolos A-L) se describen a continuación.

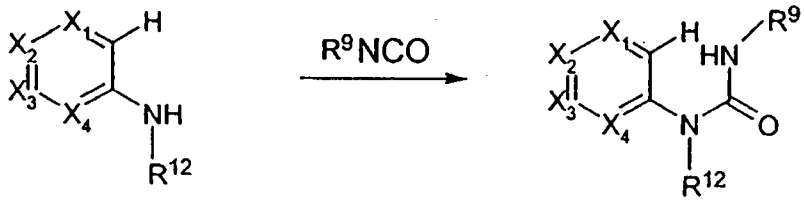
El solvente, el tiempo de reacción, la temperatura, el catalizador si hubiera, pueden variarse en todos los pasos descriptos a continuación para todas las vías, como lo apreciará el experto.

Protocolo A

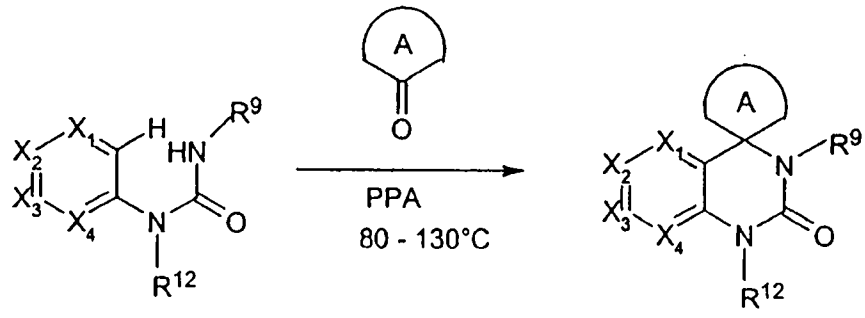
Esquema 1



(paso 1)



(paso 2)



(paso 3)

En el esquema 1, X_1, X_2, X_3, X_4, A, R^9 y R^{12} son lo definido en el resumen de la invención.

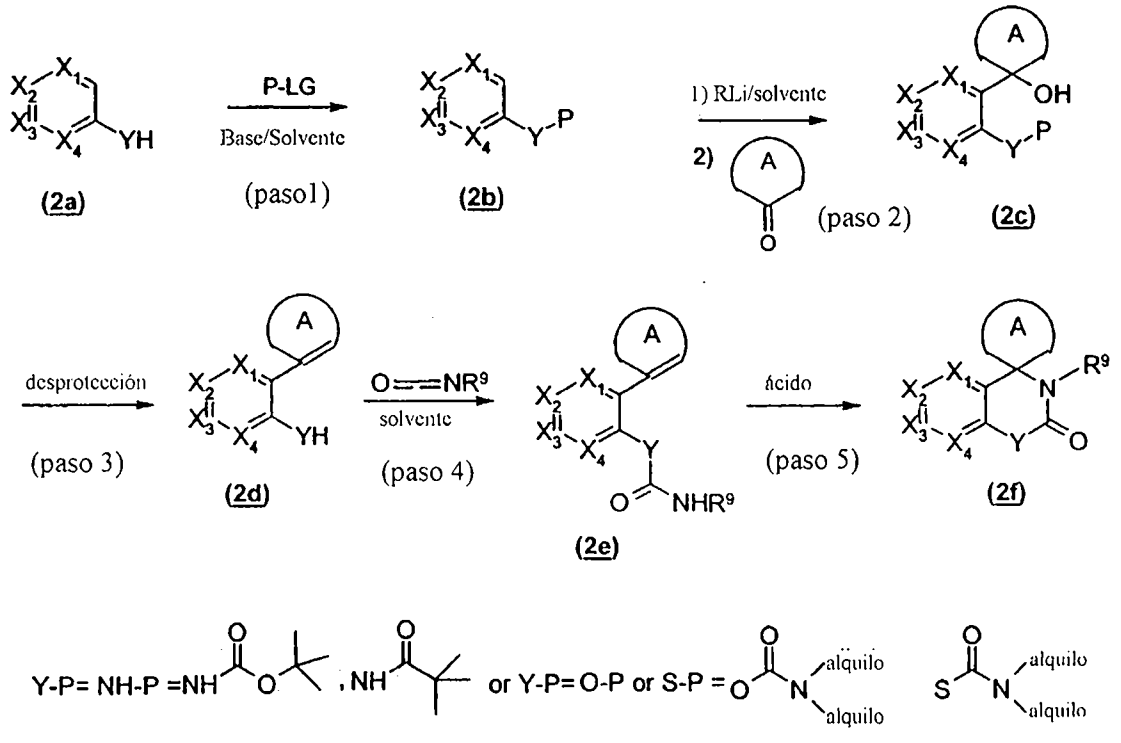
Los materiales iniciales están comercialmente disponibles o se pueden preparar de acuerdo con las vías conocidas por el

experto. Si la urea inicial del paso 3 no está comercialmente disponible, se puede preparar tratando el isocianato correspondiente con una amina primaria en un solvente tal como tetrahidrofurano (paso 1) o tratando la anilina correspondiente con un isocianato sustituido en un solvente orgánico tal como diclorometano o acetonitrilo (paso 2).

En el paso 3, la urea es convertida en la quinazolinona deseada mediante la reacción con una cetona cíclica en ácido polifosfórico a 80°C-130°C.

Protocolo B:

Esquema 2



En el esquema 2, X_1, X_2, X_3, X_4, A y R^9 son lo definido en el resumen de la invención, Y puede ser O, S o NH y LG es un grupo saliente y R es alquilo inferior.

Los compuestos iniciales están comercialmente disponibles o pueden prepararse de acuerdo con las vías conocidas por el experto.

En el paso 1, el compuesto (2a) reacciona con cloruro de dialquil-carbamoilo para formar el N,N dialquil-carbamato o tiocarbamato deseado de acuerdo con las vías conocidas por el experto. Ver Poirier, M. ; Simard, M. ; Wuest, J.D. ; *Organometallics*, 1996, 15 (4), 1296-1300.

Pueden usarse otros grupos protectores como grupos de metalización dirigida basados en oxígeno tales como OMe, OMOM, $OP(OR_2)$, $OPO(NMe)_2$. Ver Snieckus, *Chem. Rev.*, 1990, 90, 879-933.

El derivado de anilina se protege como un *t*-butil carbamato o como una pivaloil amida de acuerdo con las vías conocidas por el experto. Ver *Tet. Lett.*, 1994, 35(48), 9003-9006.

En el paso 2, el compuesto (2b) es convertido en una sal de litio (cuando Y es O o S) o en una sal de dilitio de ella

mediante la reacción con un exceso de agente formador de compuestos de litio tal como *t*-butillitio en un solvente mezclado de éter anhidro (por ejemplo, dietil éter y tetrahidrofurano) y alcano (por ejemplo pentano), y la reacción con una cetona aproprada. La reacción se lleva a cabo a baja temperatura (entre -78°C y 0°C) para dar el alcohol terciario deseado. El intermedio de organolitio también se puede formar mediante un intercambio de halógeno-metal. El organolitio también se puede transmetalizar en otro ractivo organometálico tal como un cerato (con tricloruro de cerio anhidro por ejemplo) antes del tratamiento con la cetona.

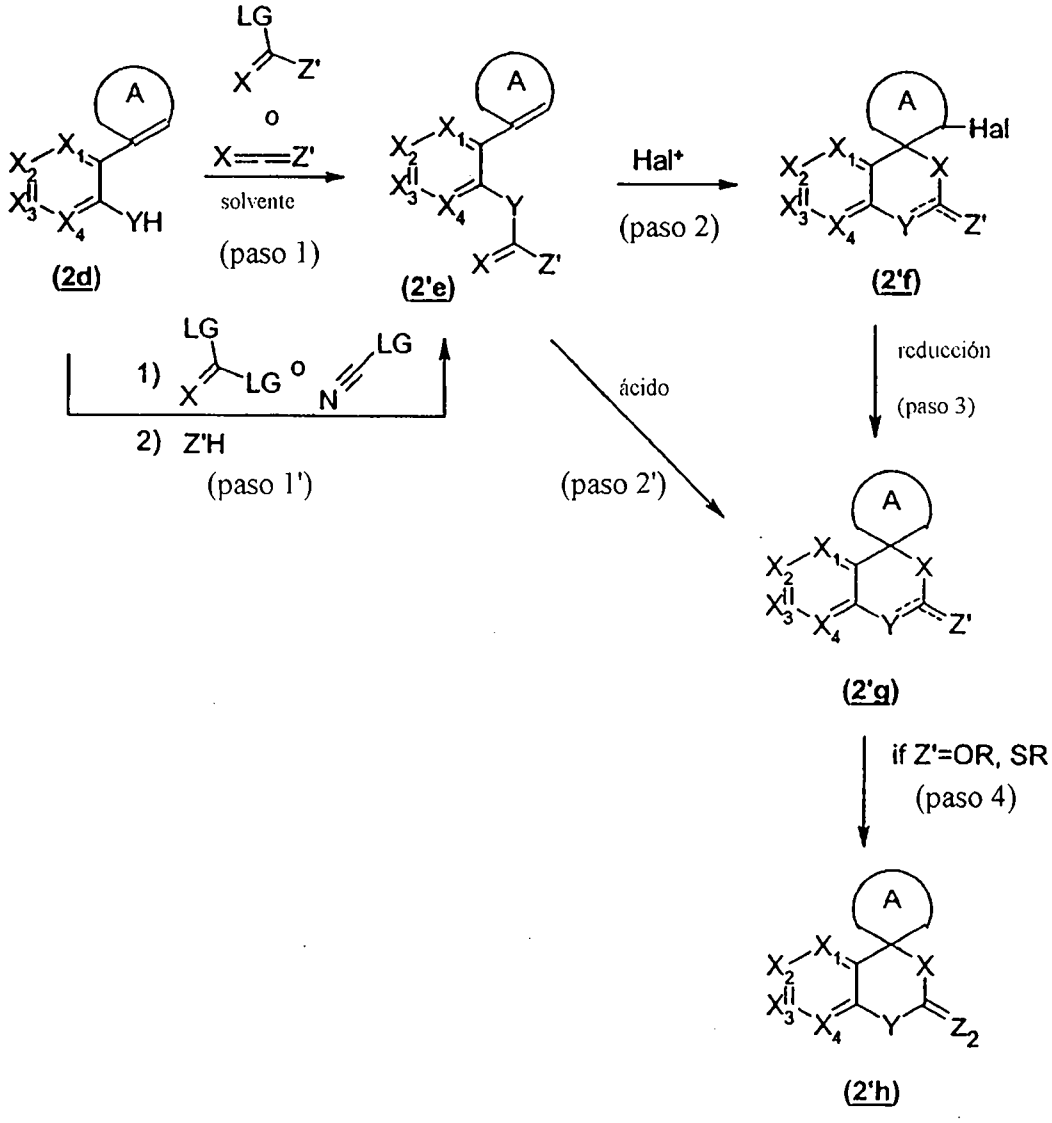
En el paso 3, el grupo protector se remueve de acuerdo con las vías conocidas por el experto en condiciones reductoras (cuando Y = O-P o S-P), en condiciones ácidas o en condiciones básicas para dar el compuesto (2d).

En el paso 4, el compuesto (2d) reacciona con un isocianato sustituido apropiado para obtener el compuesto (2e).

En el paso 5, el tratamiento del compuesto (2e) con un ácido (ácido mineral o ácido de Lewis) dispara la ciclación para dar el compuesto (2f).

Protocolo B:

Esquema 2'



En el esquema 2', X_1, X_2, X_3, X_4 y A son lo definido en el resumen de la invención, Y puede ser O, S o NR^{12}, X puede ser O, S, NR^9 y LG es un grupo saliente, Z' puede ser OR, SR, $NR^{16}R^{17}$ o NR^{13}, Hal es halógeno, Z^2 puede ser O o S y donde R^{12},

R^{13}, R^{16}, R^{17} y R^{9} son lo definido en el resumen de la invención y R es alquilo o bencilo.

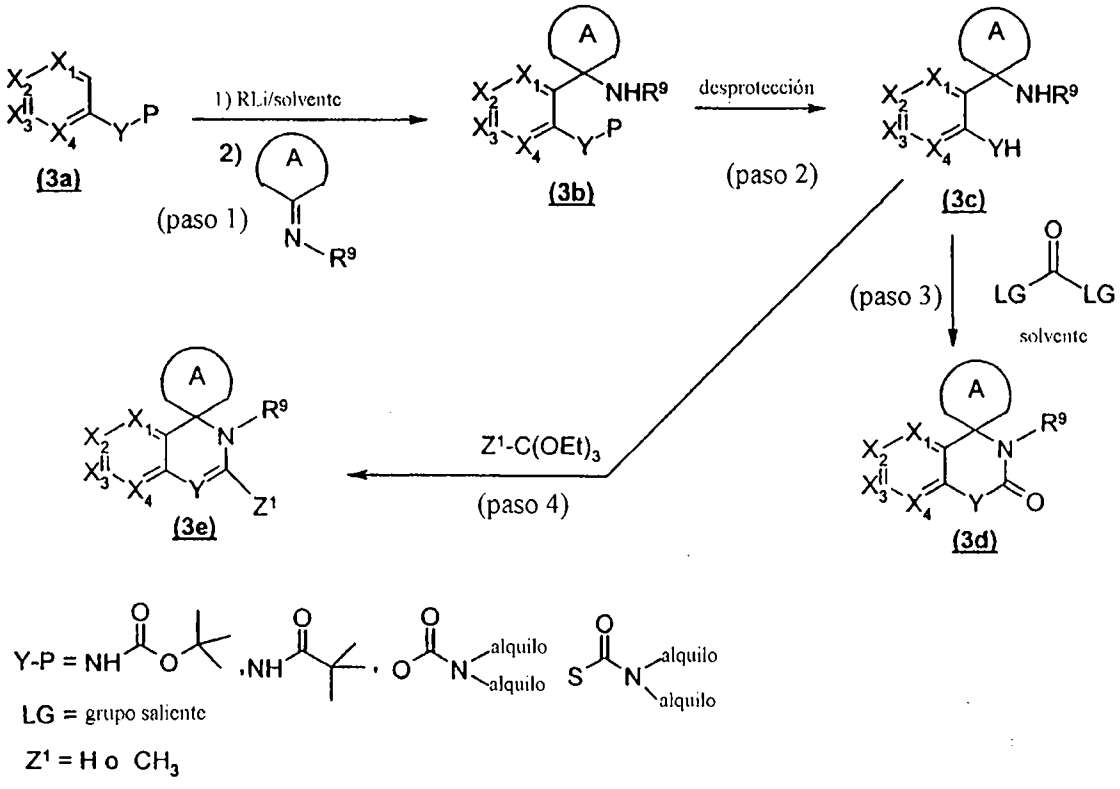
En el paso 1, el intermedio **2d** obtenido de acuerdo con el protocolo B reacciona con un derivado de carbonilo tal como un carbonato, un cloroformato, un isocianato; un derivado de tiocarbonilo tal como un isotiocianato, un tionocloroformato, u otros tales como cianamida, nitrato de 3,5-dimetil-1H-pirazol-1-carboximidamida, S-metilisotiourea o un equivalente. Alternativamente, como se muestra en el paso 1', el intermedio **2'e** se puede preparar en dos pasos tratando **2d** con bromuro de cianógeno o un derivado de carbonilo (o tiocarbonilo) activado por dos grupos salientes tales como fosgeno (o tiofosgeno), 1,1'-carbonildiimidazol (o 1,1'-tiocarbonildiimidazol), nitrofenilcloroformato o disulfuro de carbono, seguido por el agregado de un nucleófilo tal como una amina, un alcohol o un tiol para introducir Z'. Las condiciones apropiadas de la reacción para cada vía pueden ser fácilmente determinadas por el experto. Cuando se desee, ciertos intermedios **2'e** obtenidos pueden derivarse en otros intermedios **2'e** de acuerdo con las vías conocidas por el experto. Por ejemplo, un intermedio tiourea **2'e** donde Y=NH, X=S y $Z'=NH_2$ se pueden tratar con un haluro de alquilo R-X de acuerdo con las condiciones de reacción conocidas por el experto para dar un intermedio **2'e** en donde Y=NH, X=NH y Z'=SR.

En el paso 2, el intermedio **2'e** es tratado con una fuente de halonio tal como yodo, N-yodosuccinimida, bromo o N-bromosuccinimida para dar el intermedio **2'f**. En forma similar a **2'e**, el intermedio **2'f** puede derivarse en diferentes intermedios **2'f** de acuerdo con las vías conocidas por el experto. El haluro **2'f** puede reducirse a **2'g** como se muestra en el paso 3 en las condiciones de la reacción conocidas por el experto, tales como el tratamiento con trialquil hidruro de estaño y un radical iniciador como azobisisobutironitrilo (AIBN) en un solvente orgánico inerte. Alternativamente, como se muestra en el paso 2', el intermedio **2'e** puede ser directamente transformado en **2'g** en un tratamiento ácido de acuedo con las condiciones que determine el experto. Si es necesario, el intermedio **2'g** también puede derivarse en diferentes **2'g** de acuerdo con las vías conocidas por el experto. Cuando Z' es OR o SR, el intermedio **2'g** puede ser convertido en **2'h** como se muestra en el paso 4. Esto se puede hacer de acuerdo con las condiciones conocidas por el experto mediante hidrólisis en medios ácidos acuosos o mediante hidrogenólisis cuando R es bencilo.

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Protocolo C

Esquema 3



En el esquema 3, X_1, X_2, X_3, X_4 y A son lo definido en el resumen de la invención, R^9 es alquilo, arilo, alquilsulfonilo o arilsulfonilo, R es alquilo inferior e Y puede ser O, S o NH.

Un método alternativo de preparación del compuesto de la presente invención se muestra a continuación y avanza hasta la reacción del intermedio organolitio con una imina.

En el paso 1, el compuesto (3a) es convertido en una sal de litio (cuando Y es O o S) o en una sal de dilitio (cuando Y es NH) de ella mediante la reacción con un exceso de un agente formador de litio tal como *t*-butillitio en un solvente mezclado de éter anhidro (por ejemplo, dietil éter y tetrahidrofurano) y alcano (por ejemplo pentano). El organolitio resultante reacciona con una imina apropiada a baja tempe para dar la amina terciaria esperada (3b). El organolitio también puede ser transmetalizado en otro reactivo organometálico tal como un cerato (con tricloruro de cerio anhidro por ejemplo) antes del tratamiento con la cetona.

En el paso 2, el grupo protector se remueve de acuerdo con las vías conocidas para el experto en condiciones reductoras (cunado Y = O-P o S-P), en condiciones ácidas o en condiciones básicas para dar el compuesto (3c). Cuando R^9 es alquil o arilsulfonilo, este grupo se puede desproteger en el derivado de NH mediante métodos reductores o hidrólisis de acuerdo con los métodos conocidos por el experto.

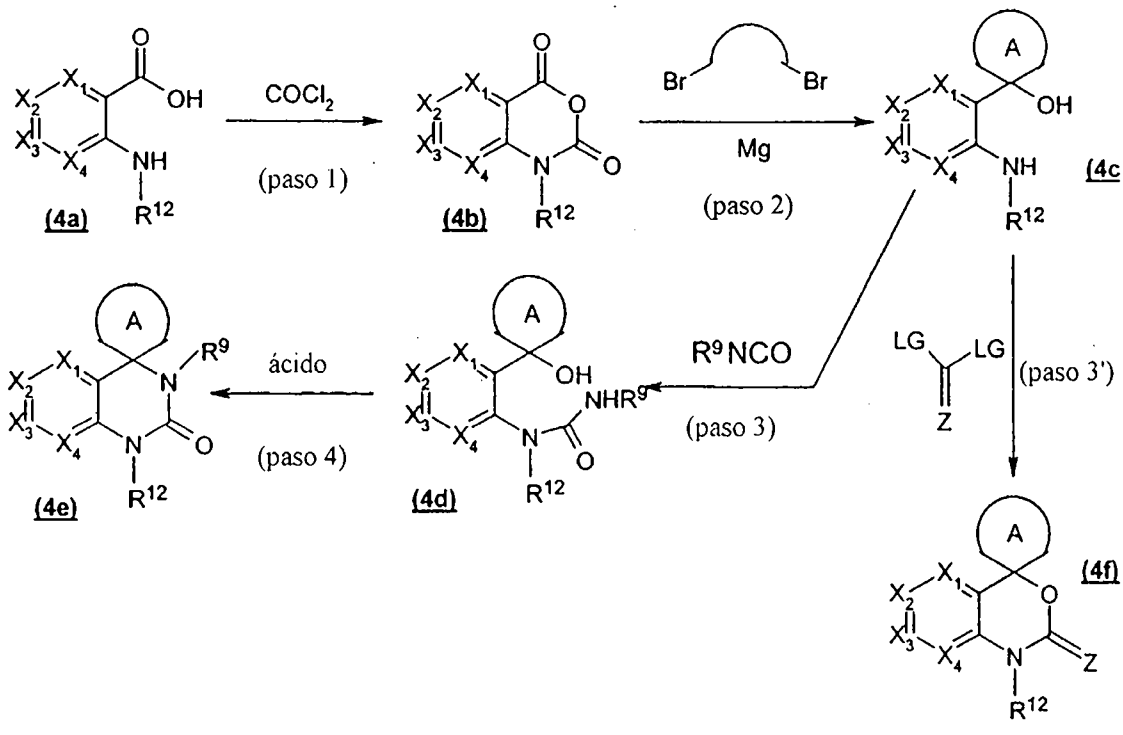
En el paso 3, el compuesto (3c) reacciona con un compuesto seleccionado de un haluro de ácido carbónico tal como fosgeno un diéster de ácido carbónico, 1,1'-carbonildiimidazol y así sucesivamente para obtener el compuesto (3d).

En el paso 4, el compuesto (3c) reacciona con un ortoéster,

en la presencia de un ácido para obtener el compuesto (3e) o sus formas tautoméricas.

Protocolo D

Esquema 4



En el esquema 4, X_1, X_2, X_3, X_4, A, R^9 y R^{12} son lo definido en el resumen de la invención, Z es O o S.

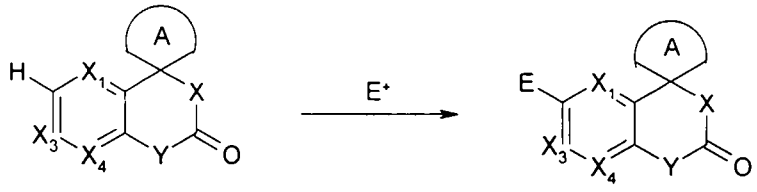
Los materiales iniciales están comercialmente disponibles o pueden prepararse de acuerdo con las vías conocidas por los expertos. En el paso 1, el ácido antranílico inicial se trata con fosgeno o una fuente de carbonilo equivalente tal como trifosgeno o carbonil diimidazol. Se pueden usar diversos

solventes y condiciones de reacción y serán fácilmente determinados por el experto. El anhídrido isatoico resultante es tratado con el reactivo de Grignard obtenido de un dihaluro y magnesio en un solvente tal como tetrahidrofurano o éter (paso 2). En el paso 3, la anilina es convertida en una urea mediante el tratamiento con un isocianato sustituido. Pueden usarse diversos solventes y condiciones de reacción y éstos serán fácilmente determinados por el experto. Por ejemplo, la reacción se puede realizar a temperatura ambiente en un solvente inerte tal como diclorometano, acetonitrilo o tetrahidrofurano en la presencia o no de una base tal como trietilamina o piridina. En el paso 4, la hidroxi-urea resultante es sometida a un ácido con o sin un solvente orgánico. Por ejemplo, la reacción puede llevarse a cabo a 70°C-90°C en ácido sulfúrico. Se puede agregar un solvente tal como tolueno o ácido acético.

En el paso 3', el compuesto 4c es convertido en el compuesto 4f mediante el tratamiento con un derivado de carbonilo (o tiocarbonilo) activado por dos grupos salientes tales como fosgeno (o tiofosgeno), 1,1'-carbonildiimidazol (o 1,1'-tiocarbonildiimidazol).

Protocolo E

Esquema 5

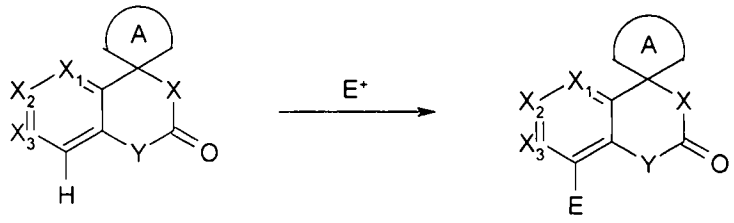


En el esquema 5, X_1, X_3, X_4, X, Y y A son lo definido en el resumen de la invención.

El compuesto tricíclico inicial reacciona con un electrófilo E^+ tal como halonio o acilio en presencia o no de un agente activador en un solvente orgánico. Pueden usarse diversos solventes y condiciones de reacción para esta sustitución aromática electrófila según el electrófilo y éstos pueden ser determinados fácilmente por el experto. Por ejemplo, el material inicial puede ser tratado con una fuente de halonio tal como N-yodo o N-bromosuccinimida en dimetilformamida a 60°C-70°C para dar el haluro correspondiente. En otro ejemplo, el material inicial reacciona con un haluro de acilo y tricloruro de aluminio, como el ácido de Lewis, en un solvente tal como dicloroetano a 80°C.

Protocolo F

Esquema 6

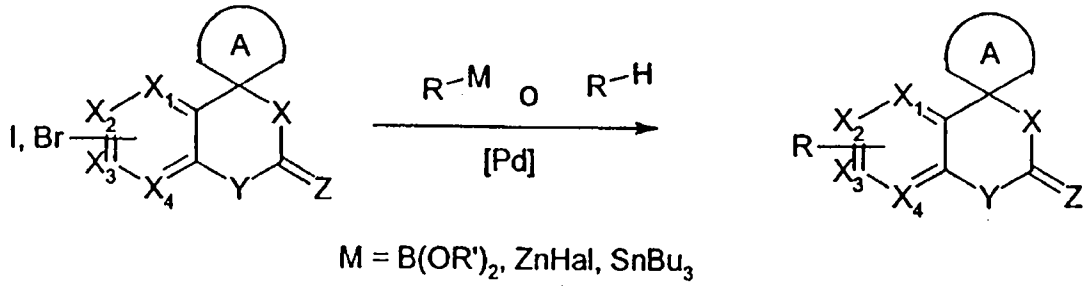


En el esquema 6, X_1, X_3, X, Y y A son lo definido en el resumen de la invención y X_2 no es CH.

El compuesto tricíclico inicial reacciona con un electrófilo E^+ en presencia o no de un agente activador en un solvente orgánico. Esta sustitución aromática electrófila es similar al Protocolo E excepto que en este caso, como X_2 es diferente de CH, la sustitución se orienta a la posición 8. En forma similar al Protocolo E, pueden usarse diversos solventes y condiciones de reacción para esta sustitución aromática electrófila según el electrófilo y éstos serán determinados fácilmente por el experto.

Prtotocolo G

Esquema 7



$M = B(OR')_2$, ZnHal, $SnBu_3$

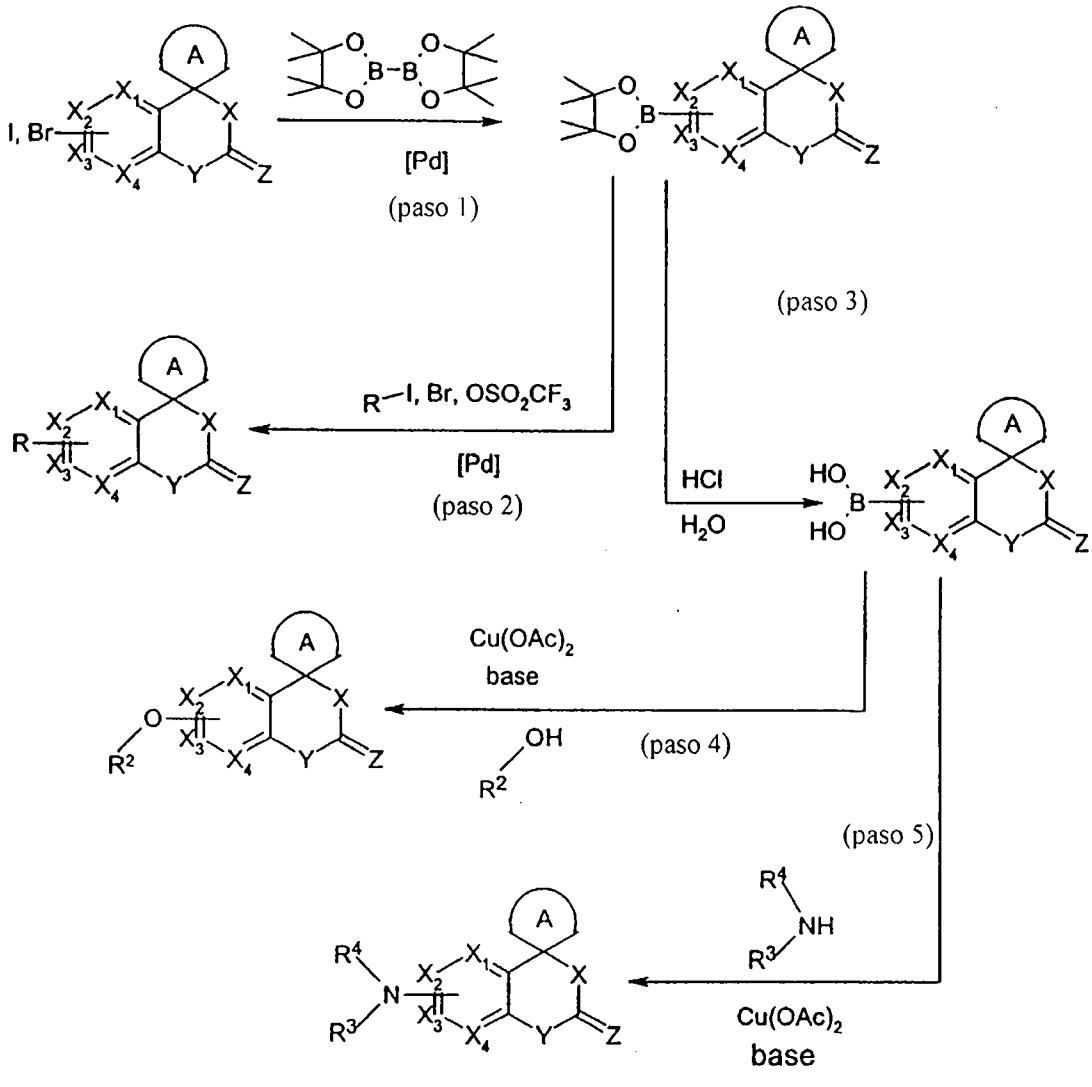
En el esquema 7, X_1, X_2, X_3 y X_4, X, Y, Z y A son lo definido en el resumen de la invención, R es alquenilo, alquinilo, arilo o heteroarilo y R' es H o alquilo.

El yoduro o bromuro de arilo o heteroarilo inicial iodide es sometido a una reacción de acoplamiento cruzado catalizada con paladio con una especie organometálica, tal como un éster de boronato, un ácido borónico, un organozinc (Hal = halógeno)o un trialquilestanano en la presencia de una base cuando sea necesario. La especie organometálica puede ser reemplazada con un alqueno o alquino terminal en la reacción de acoplamiento. Cuando se usa un alquino, se puede agregar una fuente de cobre(I), tal como yoduro de cobre. Se puede usar diversos catalizadores de paladio, solventes y condiciones de reacción para las reacciones de acoplamiento y éstas serán fácilmente determinadas por el experto. Por ejemplo, el yoduro o bromuro de arilo o heteroarilo inicial pueden reaccionar con un ácido borónico en dimetilformamida a 80°C en la presencia de

tetrakis(trifenilfosfino)paladio como catalizador y una solución acuosa de carbonato de potasio como base.

Protocolo H

Esquema 8



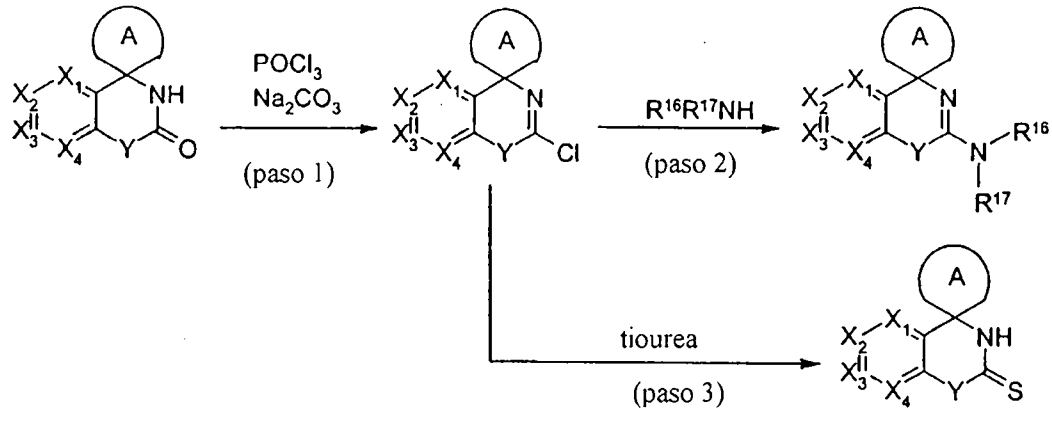
In scheme 8, X_1, X_2, X_3, X_4, X, Y, Z, R^2, R^3, R^4 and A are as defined in the summary of the invention and R is selected from aryl, alkenyl, alkynyl or heteroaryl.

En el paso 1, el yoduro o bromuro de arilo o heteroarilo inicial es tratado con bis(pinacolato)diboro antes de la catálisis con paladio para dar el éster de boronato correspondiente. Pueden usarse diversos catalizadores de paladio, solventes y condiciones de reacción y éstos serán determinados fácilmente por el experto. Por ejemplo, el yoduro o bromuro de heteroarilo inicial puede reaccionar con bis(pinacolato)diboro en dimetilformamida a 80°C en la presencia de tetrakis(trifenilfosfina) paladio como catalizador. El éster de boronato resultante luego se acopla a un yoduro, bromuro o triflato de arilo, alquenilo, alquinilo o heteroarilo catalizado por una especie de paladio (paso 2). Nuevamente, pueden usarse diversos catalizadores de paladio, solventes y condiciones de reacción para estas reacciones de acoplamiento y éstas serán fácilmente determinadas por el experto. Por ejemplo, el éster de boronato reacciona con un yoduro de arilo, alquenilo, alquinilo o heteroarilo en dimetilformamida a 80°C en la presencia de acetato de sodio como base y tetrakis(trifenilfosfina)paladio como catalizador para dar el producto acoplado.

En el paso 3, el éster de boronato se hidroliza hacia el ácido borónico correspondiente. Esto se puede hacer tratándolo con ácido, ej. una solución acuosa de ácido clorhídrico, en un solvente orgánico, ej. metanol. El ácido borónico resultante se acopla, (paso 4), bajo aire con fenol o alcohol heteroarílico, o (paso 5) con una amina primaria o secundaria, heteroarilamina, anilina, amida, sulfonamida, urea, carbamato o imida, en la presencia de una base tal como trietilamina o piridina y una fuente de cobre(II) tal como acetato de cobre(II) en un solvente como diclorometano. Pueden agregarse tamices moleculares, 4Å o 3Å, a la mezcla de la reacción.

Protocolo I

Esquema 9



En el esquema 9, X_1, X_2, X_3 y X_4, Y, R^{16}, R^{17} y A son lo definido en el resumen de la invención.

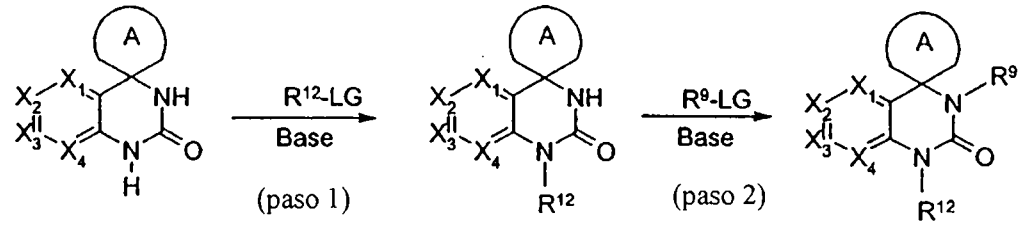
En paso 1, urea, carbamato o tio carbamato es convertido inicialmente en una haloimina a través de un agente de cloración tal como $POCl_3$ que luego reacciona nuevamente (paso 2) con una amina adecuada para formar el compuesto final. La reacción puede llevarse a cabo sin solvente o en un solvente, por ejemplo un alcohol tal como etanol, a una temperatura de entre 40°C y 80°C o bajo presión para una amina volátil, por ejemplo.

En el paso 3, la halo-imina se transforma en el derivado de tio con tiourea.

El proceso del esquema 9 precedente también puede aplicarse a los compuestos de la fórmula (I) en donde Y es NH y X es N-R^9.

Protocolo J

Esquema 10



En el esquema 10, X_1, X_2, X_3, X_4, R^9, R^{12} y A son lo definido en el resumen de la invención y LG es un grupo saliente tal como sulfonato de trifluorometano, mesilato o halógeno.

En el paso 1, la quinazolinona reacciona con R^{12}-LG para obtener la quinazolina N-sustituida.

En el paso 2, la quinazolinona N-sustituida reacciona con R^9-LG.

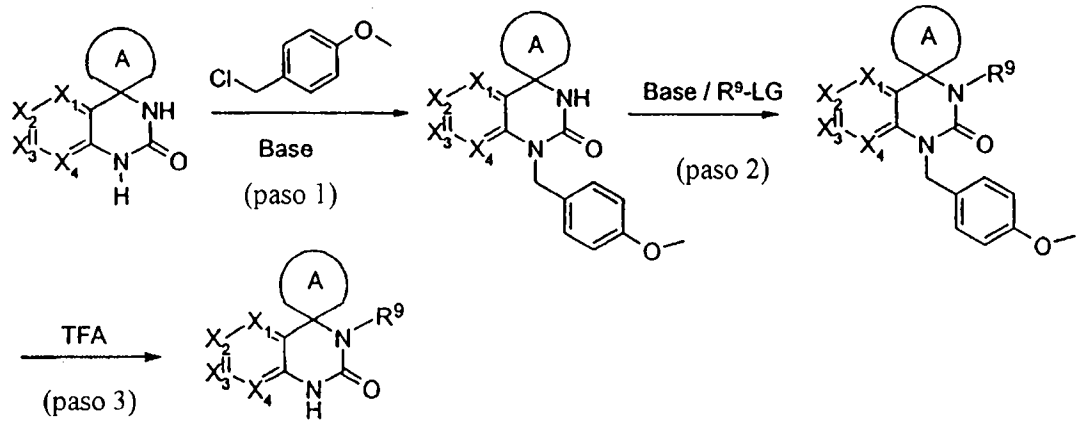
Se pueden usar diversos solventes, condiciones de operación y bases y éstas serán determinadas fácilmente por el experto. Por ejemplo, y sin ninguna limitación, se puede usar para la reacción hidruro de sodio o carbonato de cesio como base en dimetilformamida como solvente.

El paso 2 del proceso precedente puede aplicarse también a los compuestos de la fórmula (I) en donde Y es O o S.

El paso 1 del proceso precedente también puede aplicarse a los compuestos de la fórmula (I) en donde X es O o S.

Protocolo K

Esquema 11



En el esquema 11, X_1, X_2, X_3, X_4, R^9 y A son lo definido en el resumen de la invención y LG es un grupo saliente tal como sulfonato de trifuorometano, mesilato o halógeno.

En el paso 1, la quinazolinona reacciona con cloruro de parametoxi-bencilo (PMB). Se puede usar otro grupo protector. Pueden usarse diversos solventes, condiciones de operación, bases y éstos serán fácilmente determinados por el experto. Por ejemplo, y sin ninguna limitación, se puede usar para la reacción carbonato de cesio como base en dimetilformamida como solvente.

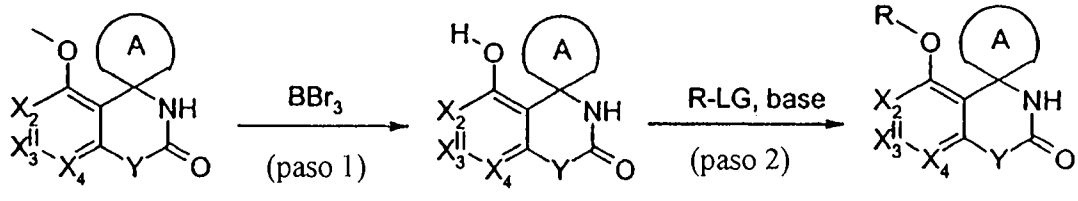
En el paso 2, la quinazolinona protegida reacciona con R^9-LG. Pueden usarse diversos solventes, condiciones de operación, bases y éstos serán fácilmente determinados por el experto.

Por ejemplo, y sin ninguna limitación, se puede usar para la reacción hidruro de sodio como base en dimetilformamida como solvente.

En el paso 3, el tratamiento con TFA de la quinazolinona protegida con N1-PMB removió el grupo protector. Se pueden usar otros grupos protectores y condiciones de desprotección.

Protocolo L

Esquema 12



En el esquema 12, X_2, X_3, X_4, y A e Y son lo definido en el resumen de la invención, R es alquilo o C(=O)-alquilo y LG es un grupo saliente.

En el paso 1, el derivado de metoxi inicial se desmetila con tribromuro de boro en un solvente tal como diclorometano. El intermdio fenol resultante es tratado en el paso 2 con un electrófilo tal como un haluro de alquilo, un haluro de acilo o similares en la presencia de una base tal como carbonato de

potasio, carbonato de cesio o hidruro de sodio en un solvente como dimetilformamida.

Ejemplos de Síntesis

Los Ejemplos 1 a 100 representan, sin limitarla, la síntesis de compuestos particularmente activos de la fórmula (I) de acuerdo con la invención.

En los siguientes protocolos experimentales, los datos de resonancia magnética nuclear (NMR) protónica se obtuvieron con un aparato de RMN de 400 MHz a menos que se indique específicamente.

Ejemplo 1

Espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A. Se agregó fenil urea (13,6 g, 0,1 mol) en porciones a una solución de ácido polifosfórico (100 g) agitado a 100°C. Después de completar la disolución de la urea, se agregó ciclohexanona (10,3 mL, 0,1 mol) gota a gota a la mezcla caliente. La mezcla se agitó a 100°C-120°C hasta que se completó y se vertió en agua fría. El precipitado se filtró,

se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. El material crudo se purificó mediante cristalización en etanol. El compuesto del título se obtuvo como un polvo blanco. Punto de fusión (mp) = 224°C-226°C.

^1H NMR [$(CD_3)_2SO$] δ 9,11 (br s, 1H, NH), 7,24 (d, *J* = 7,6 Hz, 1H), 7,09 (t, *J* = 7,9 Hz, 1H), 6,88 (t, *J* = 7,6 Hz, 1H), 6,78 (d, *J* = 7,9 Hz, 1H), 6,74 (br s, 1H, NH), 1,79-1,63 (m, 7H), 1,50 (m, 2H),), 1,20 (m, 1H).

Ejemplo 2

6'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-O-CH_3, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 4-metoxifenil urea (30 g, 0,18 mol) y ciclohexanona (18,6 mL, 0,18 mol) en ácido polifosfórico (200 mL). El precipitado se filtró, se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. The crude material was purified by crystallization in ethanol. El

material crudo se purificó mediante cristalización en etanol. El compuesto del título se obtuvo como un polvo blanco (8,2 g, 18% de rendimiento). Punto de fusión = 233°C-235°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,94 (br s, 1H, NH), 6,80 (br s, 1H), 6,72 (m, 2H), 6,61 (m, 1H), 3,69 (s, 3H), 1,76-1,47 (m, 9H), 1,23 (m, 1H).

Ejemplo 3

Espiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=CH, A=cicloheptilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando fenil urea (27,2 g, 0,2 mol) y cicloheptanona (23,5 mL, 0,2 mol) en ácido polifosfórico (200 mL). El precipitado se filtró, se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH solution. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. El material crudo se purificó mediante cristalización en etanol. El compuesto del título se obtuvo como un polvo blanco (14,7 g, 32% de rendimiento) Punto de fusión = 198-200°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,11 (br s, 1H, NH), 7,21 (d, *J* = 7,6 Hz, 1H), 7,09 (d, *J* = 7,6 Hz, 1H), 6,88 (m, 2H), 6,78 (d, *J* = 7,9 Hz, 1H), 1,94-1,72 (m, 6H), 1,54 (m, 6H).

Ejemplo 4

7'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=C-O-CH_3, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 3-metoxifenil urea (33,2 g, 0,2 mol) y ciclohexanona (20,7 mL, 0,2 mol) en ácido polifosfórico (200 mL). El precipitado se filtró, se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. El material crudo se purificó mediante cristalización en etanol. El compuesto del título se obtuvo como un polvo blanco (9,8 g, 20% de rendimiento) Punto de fusión = 228°C-230°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,03 (br s, 1H, NH), 7,13 (d, *J* = 8,5 Hz, 1H), 6,74 (br s, 1H, NH), 6,45 (dd, *J* = 8,5, 2,3 Hz, 1H), 6,36 (d, *J* = 2,3 Hz, 1H), 3,68 (s, 3H), 1,78-1,59 (m, 7H), 1,47 (m, 2H), 1,20 (m, 1H).

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Ejemplo 5

6'-Fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-fenilo, X_3=CH, X_4=CH, A=cicloheptilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 4-fenil-fenil urea (42,4 g, 0,2 mol) y cicloheptanona (23,5 mL, 0,2 mol) en ácido polifosfórico (400 g). El precipitado se filtró, se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. El material crudo se purificó mediante cristalización en etanol. El compuesto del título se obtuvo como un polvo blanco (23,3 g, 38% de rendimiento). Punto de fusión = 180°C-182°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,28 (br s, 1H, NH), 7,59 (m, 2H), 7,43 (m, 4H), 7,30 (m, 1H), 7,0 (br s, 1H, NH), 6,88 (m, 1H), 2,01 (m, 2H), 1,89 (m, 2H), 1,77 (m, 2H), 1,58 (m, 6H).

Ejemplo 6

8'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-O-CH_3, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-metoxifenil urea (49,8 g, 0,3 mol) y ciclohexanona (31 mL, 0,3 mol) en ácido polifosfórico (600 g). El precipitado se filtró, se lavó con agua fría, se recogió en etanol caliente y se neutralizó con una solución de NH_4OH. Se agregó agua para formar una solución de etanol/agua al 50% y el precipitado se filtró, se lavó con agua y se secó. El material crudo se purificó mediante cristalización en isopropanol. El compuesto del título se obtuvo como un polvo blanco (48,1 g, 65% de rendimiento). Punto de fusión = 209°C-211°C.

^1H NMR [$(CD_3)_2SO$] δ 7,79 (br s, 1H, NH), 6,87 (m, 4H), 3,79 (s, 3H), 1,79-1,60 (m, 7H), 1,48 (m, 2H), 1,22 (m, 1H).

Ejemplo 7

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-clorofenil urea (51,15 g, 0,3 mol) y ciclohexanona (29,4 g, 0,3 mol) en ácido polifosfórico (600 g). El precipitado se filtró, se lavó con agua fría y se recristalizó desde acetato de etilo. El compuesto del título se obtuvo como

un sólido naranja (21% de rendimiento). Punto de fusión = 209°C-211°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,42 (br s, 1H, NH), 7,29 (d, *J* = 7,9 Hz, 2H), 7,16 (br s, 1H, NH), 6,95 (t, *J* = 7,9 Hz, 1H), 1,81 - 1,61 (m, 7H), 1,52-1,39 (m, 2H), 1,25-1,22 (m, 1H).

Ejemplo 8 y Ejemplo 9

7'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (Ejemplo 8)

X_1=CH, X_2=CH, X_3=C-Cl, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

y 5'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (Ejemplo 9)

X_1=C-Cl, X_2=CH, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

Los compuestos del título se prepararon de acuerdo con el protocolo A, usando 3-clorofenil urea (0,51 g, 3 mmol) y ciclohexanona (0,5 mL, 4,8 mmol, 1,6 equiv.) en ácido polifosfórico (11 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/CH_3CN : 90/10 a 60/40) seguido por la recristalización en tolueno para dar 7'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona como un sólido blanco (110 mg, 15% de rendimiento). Punto de fusión = 254°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,28 (br s, 1H, NH), 7,27 (d, J = 8,0 Hz, 1H), 6,91-6,89 (m, 2H), 6,82 (s, 1H, NH), 1,83-1,61 (m, 7H), 1,49 (m, 2H), 1,24 (m, 1H).

y 5'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona como un sólido blanco (101 mg, 14% de rendimiento). Punto de fusión = 229°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,34 (br s, 1H, NH), 7,11 (t, J = 8,0 Hz, 1H), 6,91 (d, J = 8,0 Hz, 1H), 6,84 (br s, 1H, NH), 6,77 (d, J = 8,0 Hz, 1H), 2,60 (td, J = 13,0, 4,0 Hz, 2H), 1,82 (m, 2H), 1,64-1,49 (m, 5H), 1,22 (m, 1H).

Ejemplo 10

8'-Metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-CH_3, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando o-tolil urea (551 mg, 3,66 mmol) y ciclohexanona (430 µL, 4,15 mmol, 1,1 equiv.) en ácido polifosfórico (5 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó

mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) segudido por la recristalización en tolueno para dar 290 mg (34% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 204°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,32 (br s, 1H, NH), 7,10 (d, *J* = 7,7 Hz, 1H), 6,97 (d, *J* = 7,2 Hz, 1H), 7,10 (m, 2H), 1,82 - 1,61 (m, 7H), 1,50 (m, 2H), 1,23 (m, 1H).

Ejemplo 11

6'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-Cl, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 4-clorofenil urea (0,85 g, 5 mmol) y ciclohexanona (0,55 mL, 5,5 mmol, 1,1 equiv.) en ácido polifosfórico (29 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguido por la recristalización en tolueno para dar 79 mg (6% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 241°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,28 (br s, 1H, NH), 7,29 (d, *J* = 2,0 Hz, 1H), 7,16 (dd, *J* = 8,5, 2,5 Hz, 1H), 6,87 (br s, 1H, NH), 6,81 (d, *J* = 8,5 Hz, 1H), 1,76 - 1,60 (m, 7H), 1,49 (m, 2H), 1,25 (m, 1H).

Ejemplo 12

8'-Bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-bromofenil urea (1,075 g, 5 mmol) y ciclohexanona (0,6 mL, 5,8 mmol, 1,2 equiv.) en ácido polifosfórico (39 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguida por la recristalización en tolueno para dar 415 mg (28% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 213°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,86 (br s, 1H, NH), 7,45 (d, *J* = 8,0 Hz, 1H), 7,32 (d, *J* = 8,0 Hz, 1H), 7,17 (br s, 1H, NH), 6,90 (t, *J* = 8,0 Hz, 1H), 1,81-1,49 (m, 9H), 1,23 (m, 1H).

Ejemplo 13

8'-Fluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-F, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-fluorofenil urea (0,77 g, 5 mmol) y ciclohexanona (0,55 mL, 5,5 mmol, 1,1 equiv.) en ácido polifosfórico (20 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 95/5) y luego la recristalización en tolueno para dar 272 mg (23% de rendimeinto) del compuesto del título. Punto de fusión = 221°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,12 (br s, 1H, NH), 7,11 (d, J = 7,8 Hz, 1H), 7,05 (m, 1H), 6,94 (br s, 1H, NH), 6,90 (m, 1H), 1,81-1,61 (m, 7H), 1,50 (m, 2H), 1,25 (m, 1H).

Ejemplo 14

6'-Metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-CH_3, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 4-metilfenil urea (1,5 g, 10 mmol) y ciclohexanona (1,1 mL, 11 mmol, 1,1 equiv.) en ácido polifosfórico (38 g).

La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguido por la recristalización en tolueno para dar 405 mg (18% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 229°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,01 (br s, 1H, NH), 7,05 (s, 1H), 6,91 (d, *J* = 8,0 Hz, 1H), 6,68-6,66 (m, 2H), 2,22 (s, 3H), 1,76 - 1,61 (m, 7H), 1,50 (m, 2H), 1,23 (m, 1H).

Ejemplo 15

5',8'-Dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-Cl, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2,5-diclorofenil urea (0,615 g, 3 mmol) y ciclohexanona (0,50 mL, 5 mmol, 1,6 equiv.) en ácido polifosfórico (15 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 92/8) seguido por la recristalización en

tolueno para dar 56 mg (7% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 243°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,35 (br s, 1H, NH), 7,35 (d, *J* = 8,5 Hz, 1H), 7,21 (br s, 1H, NH), 7,01 (d, *J* = 9,0 Hz, 1H), 2,50 (ddd, *J* = 13,5, 13,5, 4,5 Hz, 2H), 1,83 (m, 2H), 1,68-1,51 (m, 5H), 1,24 (m, 1H).

Ejemplo 16 y Ejemplo 17

6',7'-Dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (Ejemplo 16)

X_1=CH, X_2=C-Cl, X_3=C-Cl, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

y 5',6'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (Ejemplo 17)

X_1=C-Cl, X_2=C-Cl, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 3,4-diclorofenil urea (0,61 g, 3 mmol) y ciclohexanona (0,50 mL, 5 mmol, 1,6 equiv.) en ácido polifosfórico (16 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/CH_3CN : 90/10 a 60/40) seguido por la recristalización en tolueno para dar 6',7'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona como un sólido blanco (55 mg, 6% de rendimiento). Punto de fusión = 269°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,40 (br s, 1H, NH), 7,51 (s, 1H), 7,03 (br s, 1H, NH), 6,98 (s, 1H), 1,75 - 1,59 (m, 7H), 1,48 (m, 2H), 1,24 (m, 1H).

y 5',6'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona como un sólido blanco (26 mg, 3% de rendimiento). Punto de fusión = 240°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,47 (br s, 1H, NH), 7,43 (d, *J* = 8,5 Hz, 1H), 6,91 (br s, 1H, NH), 6,81 (d, *J* = 9,0 Hz, 1H), 2,64 (ddd, *J* = 13,4, 13,4, 4,4 Hz, 2H), 1,83 (m, 2H), 1,65-1,53 (m, 5H), 1,26 (m, 1H).

Example 18

6'-Fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-fenilo, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 4-fenil-fenil urea (0,67 g, 3,15 mmol) y ciclohexanona (0,50 mL, 5 mmol, 1,6 equiv.) en ácido polifosórico (16 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre

$MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguido mediante recristalización en tolueno para dar 410 mg (13% de rendimiento) del compuesto del título. Punto de fusión = 213°C

^1H NMR [$(CD_3)_2SO$] δ 9,25 (br s, 1H, NH), 7,62 (d, *J* = 7,4 Hz, 2H), 7,52 (d, *J* = 1,6 Hz, 1H), 7,42 (m, 3H), 7,30 (t, *J* = 7,3 Hz, 1H), 6,88 (d, *J* = 8,2 Hz, 1H), 6,83 (br s, 1H, NH), 1,84 - 1,79 (m, 6H), 1,63 (m, 1H), 1,53 (m, 2H), 1,30 (m, 1H).

Ejemplo 19

8'-Yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-I, A=ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-yodofenil urea (2 g, 7,6 mmol) y ciclohexanona (1 mL, 9,6 mmol, 1,25 equiv.) en ácido polifosfórico (25 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguido por la recristalización en tolueno para dar 80mg (3% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 256°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,26 (br s, 1H, NH), 7,52 (m, 1H), 7,44 (dd, *J* = 8,3, 1,6 Hz, 1H), 6,87 (br s, 1H, NH), 6,62 (d, *J* = 8,3 Hz, 1H), 1,78 - 1,62 (m, 7H), 1,54 (m, 2H), 1.,6 (m, 1H).

Ejemplo 20

8'-Bromoespiro[ciclobutano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=ciclobutilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-bromofenil urea (0,6 g, 2,8 mmol) y cyclobutanone (0,25 mL, 3,35 mmol, 1,2 equiv.) en ácido polifosfórico (22 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos se secarib sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH :99/1 a 90/10) y el polvo resultante se lavó con diisopropil éter. El compuesto del título se obtuvo como un polvo blanco (0,03 g, 4% de rendimiento). mp = 203-205°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,93 (br s, 1H, NH), 7,80 (br s, 1H, NH), 7,50 (d, *J* = 7,7 Hz, 1H), 7,47 (d, *J* = 7,7 Hz, 1H), 6,95 (t, *J* = 7,7 Hz, 1H), 2,46-2,39 (m, 4H), 1,86 (m, 2H).

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Ejemplo 21

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=cicloheptilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-bromofenil urea (0,6 g, 2,8 mmol) y cicloheptanona (0,5 mL, 4,2 mmol, 1,5 equiv.) en ácido polifosfórico (22 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH :99/1 a 90/10) y el polvo blanco resultante se lavó con diisopropil éter. El compuesto del título se obtuvo como un polvo blanco (0,12 g, 14% de rendimienot). Punto de fusión = 215°C-217°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,87 (br s, 1H, NH), 7,44 (d, *J* = 7,8 Hz, 1H), 7,31 (br s, 1H, NH), 7,28 (d, *J* = 7,8 Hz, 1H), 6,90 (t, *J* = 7,8 Hz, 1H), 1,96-1,84 (m, 4H), 1,76-1,71 (m, 2H), 1,56 (m, 6H).

Ejemplo 22

8'-Bromo-4-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A=4-metil-ciclohexilo, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-bromofenil urea (0,6 g, 2,8 mmol) y 4-metilciclohexanona (0,41 mL, 3,.35 mmol, 1,2 equiv.) en ácido polifosfórico (22 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH :99/1 a 90/10) y el polvo resultante se lavó con diisopropil éter. El compuesto del título se obtuvo como un polvo blanco. (0,11 g, 11% de rendimiento). Punto de fusión = 187°C-189°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,85 (br s, 1H, NH), 7,44 (d, *J* = 7,8 Hz, 1H), 7,31 (d, *J* = 7,8 Hz, 1H), 7,14 (br s, 1H, NH), 6,89 (t, *J* = 7,8 Hz, 1H), 1,75 (m, 4H), 1,56-1,43 (m, 5H),), 1,85 (d, *J* = 6,2 Hz, 3H).

Ejemplo 23

8'-Bromoespiro[biciclo[3,2,1]octano-2-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Br, A= biciclo[3,2,1]octano, X=NH, Z=O, Y=NH.

El compuesto del título se preparó de acuerdo con el protocolo A, usando 2-bromofenil urea (0,6 g, 2,8 mmol) y biciclo[3.2.1]octan-2-ona (0,55 g, 4,47 mmol, 1,6 equiv.) en

ácido polifosfórico (22 g). La capa acuosa se extrajo con CH_2Cl_2/MeOH (2/1). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH :99/1 a 90/10) y el polvo resultante se lavó con diisopropil éter. El compuesto del título se obtuvo como un polvo blanco (0,003 g, 1% de rendimiento). Punto de fusión = 276°C-278°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,92 (br s, 1H, NH), 7,48 (d, *J* = 7,7 Hz, 1H), 7,42 (br s, 1H, NH), 7,39 (d, *J* = 7,7 Hz, 1H), 6,92 (t, *J* = 7,7 Hz, 1H), 2,33 (td, *J* = 13,8, 5,7 Hz, 1H), 2,15-2,10 (m, 3H), 1,98 (d, *J* = 11,5 Hz, 1H), 1,58-1,52 (m, 2H), 1,37-1,28 (m, 4H), 1,18 (m, 1H).

Ejemplo 24

6',8'-Dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-Cl, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solucion del Ejemplo 7 (100,2 mg, 0,4 mmol) en dimetilformamida (2 mL) fue tratada con N-clorosuccinimida (80 mg, 0,6 mmol, 1,5 equiv.) a 60°C toda la noche. La mezcla de la reacción se concentró y luego se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 100/0 a 90/10) HPLC de fase inversa (columna de C_{18}, gradiente de

acetonitrilo en agua: 50/50 a 95:5) para dar el compuesto del título como un sólido blanco (48% de rendimiento). Punto de fusión = 245°C

^{1}H NMR [($CDCl_3$] δ 7,26 (m, 1H), 7,19 (br s, 1H, NH), 7,10 (m, 1H), 5,80 (br s, 1H, NH), 1,97 (m, 2H), 1,82-1,57 (m, 7H), 1,29 (m, 1H).

Ejemplo 25

8'-Cloro-6'-yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-I, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución del Ejemplo 7 (5 g, 20 mmol) en ácido trifluoroacético (25 mL) se agregaron posteriormente N-yodosuccinimida (6 g, 22 mmol, 1,1 equiv.) y ácido sulfúrico (4 mL). La solución resultante se calentó a 55°C toda la noche, se concentró bajo presión reducida, se recogió en diclorometano y se lavó dos veces con agua. La mezcla de la reacción se concentró y se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 97/3) para dar 4,5 g (73% de rendimiento) del compuesto del título como un sólido amarillento. Punto de fusión = 261°C

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^{1}H NMR [$(CD_3)_2SO$] δ 8,64 (br s, 1H, NH), 7,64 (d, *J* = 2,0 Hz, 1H), 7,56 (d, *J* = 1,0 Hz, 1H), 7,22 (br s, 1H, NH), 1,76 - 1,59 (m, 7H), 1,49 (m, 2H), 1,25 (m, 1H).

Example 26

8'-Cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-fenilo, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solución del Ejemplo 18 (232 mg, 0,79 mmol) en dimetilformamida (4 mL) fue tratada con N-clorosuccinimida (80 mg, 0,6 mmol, 1,.5 equiv.) a 60°C toda la noche. La mezcla de la reacción se concentró y luego se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) para dar el compuesto del título como un sólido blanco (41% de rendimiento). Punto de fusión = 226°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,50 (br s, 1H, NH), 7,68 (d, *J* = 7,3 Hz, 2H), 7,60 (s, 1H), 7,56 (s, 1H), 7,44 (t, *J* = 7,1 Hz, 2H), 7,34 (m, 1H), 7,15 (br s, 1H, NH), 1,88-1,22 (m, 10H).

Ejemplo 27

8'-Cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-O-CH_3, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solución del Ejemplo 2 (500 mg, 2,03 mmol) en dimetilformamida (10 mL) fue tratada con N-clorosuccinimida (300 mg, 2,24 mmol, 1,1 equiv.) a 60°C toda la noche. La mezcla de la reacción se concentró y se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) seguido por la recristalización en tolueno para dar 76 mg (13% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 226°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,20 (br s, 1H, NH), 6,96 (br s, 1H, NH), 6,92 (m, 1H), 6,87 (m, 1H), 3,73 (s, 3H), 1,72 - 1,61 (m, 7H), 1,62 (m, 2H), 1,26 (m, 1H).

Ejemplo 28

8'-Cloro-6'-fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-fenilo, X_3=CH, X_4=C-Cl, A=cicloheptilo, X=NH, Z=O, Y=NH

Una solución del Ejemplo 5 (150 mg, 0,49 mmol) en dimetilformamida (2 mL) fue tratada con N-clorosuccinimida (75 mg, 0,56 mmol, 1,1 equiv.) a 60°C toda la noche. La mezcla de la reacción se concentró y luego se purificó mediante

cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10) para dar 158 mg (95% de rendimiento) del compuesto del título como un sólido amarillento. Punto de fusión = 201°C

^{1}H NMR [($CDCl_3$] δ 7,51-7,41 (m, 6H), 7,36 (m, 2H), 5,90 (br s, 1H, NH), 2,75-2,01 (m, 4H), 1,77-1,43 (m, 8H).

Ejemplo 29

8'-Cloro-6'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-CH_3, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solución del Ejemplo 14 (350 mg, 1,51 mmol) en dimetilformamida (7 mL) fue tratada con N-clorosuccinimida (305 mg, 2,3 mmol, 1,5 equiv.) a 60°C toda la noche. La mezcla de la reacción se concentró y luego se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 90/10). El sólido resultante se trituró con metanol para dar el compuesto del título como un sólido blanco (28% de rendimiento). Punto de fusión = 266°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,23 (br s, 1H, NH), 7,11 (m, 2H), 7,03 (br s, 1H, NH), 2,23 (s, 3H), 1,77 - 1,61 (m, 7H), 1,51 (m, 2H), 1,25 (m, 1H).

Ejemplo 30

8'-Cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(3-piridilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (0,5 g, 1,4 mmol) en dimetilformamida (5 mL) se agregaron sucesivamente ácido 3-piridilborónico (0,22 g, 1,7 mmol, 1,2 equiv.) y una solución acuosa a 2M de carbonato de potasio (1,5 mL). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakistrifenilfosfino paladio (60 mg, 0,05 mmol, 0,04 equiv.). Después de calentar a 90°C toda la noche, la mezcla se concentró bajo presión reducida, se trituró con agua y se filtró. El sólido resultante se trituró con acetato de etilo, se filtró y se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/EtOAc : 80/20 a 50/50) para dar 140 mg (30% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 246°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,93 (br s, 1H, NH), 8,55 (m, 2H), 8,10 (m, 1H), 7,71 (d, J = 1,5 Hz, 1H), 7,65 (d, J = 1,5 Hz, 1H), 7,45 (dd, J = 8,0, 5,0 Hz, 1H), 7,19 (br s, 1H, NH), 1,91 - 1,77 (m, 6H), 1,63 (m, 1H), 1,54 (m, 2H), 1,32 (m, 1H).

Ejemplo 31

8'-Cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(4-piridilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (0,5 g, 1,4 mmol) en dimetilformamida (5 mL) se agregaron sucesivamente ácido 4-piridilborónico (0,22 g, 1,7 mmol, 1,2 equiv.) y una solución acuosa a 2M de carbonato de potasio (1,5 mL). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakistrifenilfosfina paladio (60 mg, 0,05 mmol, 0,04 equiv.). Después de calentar a 90°C toda la noche, la mezcla se concentró bajo presión reducida, se lavó con agua y acetato de etilo y luego se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/EtOAc : 80/20 a CH_2Cl_2/MeOH : 97/3) para dar 40 mg (10% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 320°C-321°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,64 (br s, 1H, NH), 8,59 (d, J = 6,0 Hz, 2H), 7,80-7,72 (m, 4H), 7,22 (br s, 1H, NH), 1,99 - 1,77 (m, 6H), 1,65 (m, 1H), 1,54 (m, 2H), 1,31 (m, 1H).

Ejemplo 32

6'-(4-Carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(4-carboxifenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (1 g, 2,8 mmol) en dimetilformamida (10 mL) se agregó sucesivamente ácido 4-carboxifenilborónico (0,55 g, 3,35 mmol, 1,2 equiv.) y una solución acuosa a 2M de carbonato de potasio (3 mL). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakistrifenilfosfina paladio (120 mg, 0,1 mmol, 0,04 equiv.). Después de calentar a 90°C durante 4 horas, la mezcla se concentró bajo presión reducida, se recogió en acetato de etilo y se lavó con agua. La capa acuosa se acidificó a pH 2 y se extrajo con acetato de etilo. La capa orgánica se concentró bajo presión reducida a un tercio del volumen y se filtró. El sólido resultante se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 97/3 a 95/5) para dar 250 mg (40% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 309°C

^{1}H NMR [$(CD_3)_2SO$] δ 12,95 (br s, 1H, OH), 8,58 (br s, 1H, NH), 7,98 (d, *J* = 8,5 Hz, 2H), 7,83 (d, *J* = 8,5 Hz, 2H), 7,70 (d, *J* = 1,5 Hz, 1H), 7,65 (s, 1H), 7,20 (br s, 1H, NH), 1,93 - 1,78 (m, 6H), 1,64 (m, 1H), 1,54 (m, 2H), 1,32 (m, 1H).

Ejemplo 33

6'-(3-Carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(3-carboxifenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (1 g, 2,8 mmol) en dimetilformamida (10 mL) se agregaron sucesivamente ácido 3-carboxifenilborónico (0,55 g, 3,35 mmol, 1,2 equiv.) y una solución acuosa a 2M de carbonato de potasio (3 mL). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakistrifenilfosfina paladio (120 mg, 0,1 mmol, 0,04 equiv.). Después de calentar a reflujo toda la noche, la mezcla se concentró bajo presión reducida, se recogió en diclorometano y se lavó con agua. La capa acuosa se acidificó a pH 1 y se filtró para dar 330 mg (58% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 300°C

^{1}H NMR [$(CD_3)_2SO$] δ 13,10 (br s, 1H, OH), 8,54 (br s, 1H, NH), 8,14 (s, 1H), 7,92 (t, J = 7,5 Hz, 2H), 7,64 (d, J = 1,5 Hz, 1H), 7,59-7,55 (m, 2H), 7,17 (br s, 1H, NH), 1,89 - 1,78 (m, 6H), 1,64 (m, 1H), 1,55 (m, 2H), 1,32 (m, 1H).

Ejemplo 34

8'-Cloro-6'-(1*H*-indol-5-il)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-indol-5-ilo, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (0,5 g, 1,4 mmol) en dimetilformamida (5 mL) se agregaron sucesivamente ácido 5-indolilborónico (0,26 g, 1,6 mmol, 1,2 equiv.) y una solución acuosa a 2M de carbonato de potasio (1,5 mL). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakistrifenilfosfina paladio (60 mg, 0,05 mmol, 0,04 equiv.). Después de calentar a 80°C toda la noche, la mezcla se concentró bajo presión reducida, se recogió en acetato de etilo y se lavó tres veces con agua. El residuo se purificó luego mediante cromatografía sobre gel de sílice (CH_2Cl_2/EtOAc : 80/20) para dar 210 mg (44% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 257°C

^{1}H NMR [$(CD_3)_2SO$] δ 11,12 (br s, 1H, NH), 8,40 (br s, 1H, NH), 7,83 (s, 1H), 7,56 (m, 2H), 7,44 (d, *J* = 8,0 Hz, 1H), 7,39-7,36 (m, 2H), 7,11 (s, 1H), 6,47 (br s, 1H, NH), 1,89 - 1,78 (m, 6H), 1,64 (m, 1H), 1,55 (m, 2H), 1,32 (m, 1H).

Ejemplo 35

8'-Cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(2-piridilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución del Ejemplo 25 (0,5 g, 1,3 mmol) en tetrahidrofurano (5 mL) se agregó una solución 0,5 M de 2-piridil bromuro de zinc en tetrahidrofurano (60 µL, 30 mmol, 23 equiv.). La mezcl se desgasificó hirviendo nitrógeno durante 30 minutos y se agregó tetrakis(trifenilfosfino)paladio (60 mg, 0,05 mmol, 0,04 equiv.). Después de refluir durante 4 h, se agregó tetrakis(trifenilfosfino)paladio (100 mg) y tolueno (5 mL). Después de calentar a 90°C toda la noche, la mezcla se diluyó con diclorometano y se lavó tres veces con agua. La capa orgánica se concentró bajo presión reducida y se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/EtOAc : 90/10) para dar 50 mg (2% de rendimiento) del compuesto del título como un sólido. Punto de fusión = 251°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,64 (br s, 1H, NH), 7,45 (dd, *J* = 5,0, 1,0 Hz, 1H), 8,04-8,01 (m, 3H), 7,85 (td, *J* = 7,5, 2,0 Hz, 1H), 7,32 (m, 1H), 7,21 (br s, 1H, NH), 1,89 - 1,83 (m, 6H), 1,66 (m, 1H), 1,56 (m, 2H), 1,32 (m, 1H).

Ejemplo 36

8'-Cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexane-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(3-dimetilaminoprop-1-inilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 25 (0,5 g, 1,4 mmol) en pirrolidina (10 mL) se agregaron sucesivamente 1-dimetilamino-2-propina (0,170 mL, 1,6 mmol, 1,2 equiv.), tolueno (10 mL) y tetrakis(trifenilfosfino) paladio (80 mg, 0,07 mmol, 0,05 equiv.). Después de calentar a 45°C toda la noche, la mezcla se filtró, se diluyó con acetato de etilo y se lavó dos veces con una solución acuosa a 1 M de ácido clorhídrico. La capa acuosa se basificó a pH 9 y se extrajo dos veces con acetato de etilo. Los extractos combinados se secaron sobre sulfato de sodio, se concentraron bajo presión reducida y para dar 60 mg (13% de rendimiento) del compuesto del título como un sólido amarillento. Punto de fusión = 208°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,63 (br s, 1H, NH), 7,37 (d, J = 1,5 Hz, 1H), 7,34 (s, 1H), 7,19 (br s, 1H, NH), 3,43 (s, 2H), 2,24 (s, 6H), 1,81 - 1,72 (m, 6H), 1,62 (m, 1H), 1,50 (m, 2H), 1,27 (m, 1H).

Ejemplo 37

8'-Cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(3-metilaminoprop-1-inilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución del Ejemplo 25 (0,2 g, 0,5 mmol)) en dimetilformamida (3mL) se agregaron sucesivamente N-metilpropargilamina (0,1 mL, 1 mmol, 2 equiv.) y trietilamina (1 mL, 7 mmol, 14 equiv.). La mezcla se desgasificó hirviendo nitrógeno durante 30 minutos luego se agregó tetrakis(trifenilfosfino)paladio (20 mg, 0,025 mmol, 0,05 equiv.) y yoduro de cobre(I) (20 mg, 0,1 mmol, 0,02 equiv.). Después de calentar a 80°C toda la noche, la mezcla se diluyó con diclorometano y se lavó tres veces con agua. La capa orgánica se secó sobre sulfato de sodio, se filtró, se concentró bajo presión reducida y purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 98/2 a CH_2Cl_2/MeOH/NH_4OH : 96/3/1) para dar 40 mg (25% de rendimiento) del compuesto como un sólido. Punto de fusión = 188°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,62 (br s, 1H, NH), 7,33 (s, 1H), 7,32 (s, 1H), 7,19 (br s, 1H, NH), 3,50 (br s, 2H), 2,35 (br s, 3H), 1,76 - 1,73 (m, 6H), 1,61 (m, 1H), 1,50 (m, 2H), 1,26 (m, 1H).

Ejemplo 38

8'-Cloro-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-(4-(4-metil-piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (100 mg, 0,27 mmol) en tolueno (3 mL) se agregó cloruro de tionilo (0,03 mL, 0,4 mmol, 1,5 equiv.). La mezcla resultante se calentó a reflujo durante 2 horas, luego se concentró dos veces bajo presión reducida y se tomó en tolueno. Al sólido resultante en tolueno (2 mL) se agregó trietilamina (0,1 mL, 0,54 mmol, 2 equiv.) y 1-metilpiperazina (0,04 mL, 0,32 mmol, 1,2 equiv.). Después de agitar toda la noche, la mezcla se diluyó con diclorometano y se lavó dos veces con agua. La capa orgánica se concentró bajo presión reducida y se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 97/3) para dar 20 mg (16% de rendimiento) del compuesto de título como un sólido blanco.

Punto de fusión = 277°C

1H NMR [$(CD3)_2SO$] δ 8,55 (br s, 1H, NH), 7,80 (d, J = 8,0 Hz, 2H), 7,67 (s, 1H), 7,61 (s, 1H), 7,50 (d, J = 8,0 Hz, 2H), 7,18 (br s, 1H, NH), 3,60 (br m, 4H), 3,08 (br m, 4H), 2,67 (br s, 3H), 1,91 - 1,72 (m, 6H), 1,65 (m, 1H), 1,54 (m, 2H), 1,31 (m, 1H).

Ejemplo 39

8'-Cloro-6'-[4-(3-*N*-dimetilamino-propilcarboxamido)fenil]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-[4-(3-*N*-dimetilamino-propilcarboxamido)fenilo], X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (122 mg, 0,33 mmol) en tolueno (3 mL) se agregó cloruro de tionilo (0,04 mL, 0,5 mmol, 1,5 equiv.). La mezcla resultante se calentó a reflujo toda la noche, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (2 mL) se agregó trietilamina (0,1 mL, 0,54 mmol, 1,6 equiv.) y 3-dimetilaminopropilamina (0,037 mL, 0,26 mmol, 0,8 equiv.). Después de agitar durante 4 h, la mezcla se diluyó con diclorometano y se lavó dos veces con agua y una solución acuosa a 1N de ácido clorhídrico. La capa acuosa se basificó a pH 9 y se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida para dar 40 mg (34% de rendimiento) del compuesto del título como un sólido blanco.

Punto de fusión = 232°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,59-8,55 (m, 2H), 7,90 (d, *J* = 8,5 Hz, 2H), 7,79 (d, *J* = 8,5 Hz, 2H), 7,68 (d, *J* = 1,5 Hz, 1H), 7,63 (s, 1H), 7,18 (br s, 1H, NH), 3,29 (m, 2H), 2,26 (t, *J* = 7,0 Hz, 2H), 2,14 (s, 6H), 1,92 - 1,77 (m, 6H), 1,67 (m, 3H), 1,54 (m, 2H), 1,32 (m, 1H).

Ejemplo 40

8'-Cloro-6'-[4-(2-*N*-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-[4-(2-*N*-dimetilamino-etilcarboxamido)fenilo], X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (150 mg, 0,4 mmol) en tolueno (3 mL) se agregó cloruro de tionilo (0,03 mL, 0,41 mmol, 1,0 equiv.). La mezcla resultante se calentó a reflujo durante 3 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (3 mL) se agregó trietilamina (0,14 mL, 0,8 mmol, 2 equiv.) y 2-dimetilaminoetilamina (0,04 mL, 0,32 mmol, 0,8 equiv.). Después de agitar toda la noche, la mezcla se concentró, se diluyó con diclorometano y se lavó dos veces con agua y una solución acuosa a 1N de ácido clorhídrico. La capa acuosa se basificó a pH 9 y se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida para dar 100 mg (56% de rendimiento) del compuesto del título como un sólido blanco.

Punto de fusión = 234°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,54 (br s, 1H, NH), 8,44 (t, *J* = 5,5 Hz, 1H), 7,91 (d, *J* = 8,5 Hz, 2H), 7,79 (d, *J* = 8,5 Hz, 2H), 7,69 (d, *J* = 1,5 Hz, 1H), 7,63 (d, *J* = 1,5 Hz, 1H), 7,18 (br s, 1H, NH), 3,37 (q, *J* = 6,5 Hz, 2H), 2,45 (t, *J* = 6,5 Hz, 2H), 2,22

(s, 6H), 1,90 - 1,74 (m, 6H), 1,65 (m, 1H), 1,54 (m, 2H), 1,32 (m, 1H).

Example 41

8'-Cloro-6'-[3-(3-*N*-dimetilamino-propilcarboxamido)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-[3-(3-*N*-dimetilamino-propilcarboxamido)fenilo], X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 33 (100 mg, 0,27 mmol) en tolueno (10 mL) se agregó cloruro de tionilo (0,1 mL, 1,3 mmol, 5 equiv.). La mezcla resultante se calentó a reflujo durante 2 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (10 mL) se agregó trietilamina (0,1 mL, 0,54 mmol, 2 equiv.) y 3-dimetilaminopropilamina (0,03 mL, 0,21 mmol, 0,8 equiv.). Después de agitar durante 3 h, la mezcla se concentró, se diluyó con diclorometano y se lavó agua y una solución acuosa a 1N ácido clorhídrico. La capa acuosa se lavó con acetato de etilo, se basificó a pH 9 y se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida para dar 30 mg (30% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 208°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,60 (m, 1H), 8,54 (br s, 1H, NH), 8,03 (br s, 1H, NH), 7,83 (d, *J* = 7,5 Hz, 1H), 7,78 (d, *J* = 8,0 Hz, 1H), 7,69 (d, *J* = 1,5 Hz, 1H), 7,60 (s, 1H), 7,52 (t, *J* = 7,5 Hz, 1H), 7,17 (br s, 1H, NH), 3,29 (m, 2H), 2,27 (t, *J* = 7,0 Hz, 2H), 2,14 (s, 6H), 1,85 - 1,78 (m, 6H), 1,67 (m, 3H), 1,55 (m, 2H), 1,30 (m, 1H).

Ejemplo 42

8'-Cloro-6'-[3-(4-metil-piperazin-1-carbonil)-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-[3-(4-metil-piperazin-1-carbonil)-fenilo], X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 33 (100 mg, 0,27 mmol) en tolueno (5 mL) se agregó cloruro de tionilo (0,03 mL, 0,4 mmol, 1,5 equiv.). La mezcla resultante se calentó a reflujo durante 3 horas, luego se concentró dos veces bajo presión reducida y se tomó en tolueno. Al sólido resultante en tolueno (5 mL) se agregó trietilamina (0,1 mL, 0,54 mmol, 2 equiv.) y 1-metilpiperazina (0,024 mL, 0,21 mmol, 0,8 equiv.). Después de agitar toda la noche, la mezcla se diluyó con diclorometano y se lavó dos veces con agua. La capa orgánica se concentró bajo presión reducida, se tomó con acetato de etilo y se lavó con una solución acuosa a 1N de ácido clorhídrico. La capa capa

acuosa se lavó con acetato de etilo, se basified a pH 9 y se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida para dar 60 mg (61% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 207°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,52 (br s, 1H, NH), 7,76 (d, *J* = 8,0 Hz, 1H), 7,67 (s, 1H), 7,65 (d, *J* = 1,5 Hz, 1H), 7,58 (d, *J* = 1,5 Hz, 1H), 7,50 (t, *J* = 7,5 Hz, 1H), 7,32 (d, *J* = 7,5 Hz, 1H), 7,16 (br s, 1H, NH), 3,64 (br m, 4H), 2,32 (br m, 4H), 2,20 (s, 3H), 1,89 - 1,77 (m, 6H), 1,64 (m, 1H), 1,53 (m, 2H), 1,32 (m, 1H).

Ejemplo 43

8'-Cloro-6'-[3-(2-*N*-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=CH, X_2=C-[3-(2-*N*-dimetilamino-etilcarboxamido)fenilo], X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 33 (100 mg, 0,27 mmol) en tolueno (10 mL) se agregó cloruro de tionilo (0,1 mL, 1,3 mmol, 5 equiv.). La mezcla resultante se calentó a reflujo durante 2 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (10 mL) se agregó trietilamina (0,1 mL, 0,54 mmol, 2 equiv.) y 2-dimetilaminoetil amina (0,024 mL, 0,21 mmol, 0,8 equiv.). Después de agitar durante 3 h, la

mezla se concentró, se diluyó con diclorometano y se lavó dos veces con agua y una solución acuosa a 1N de ácido clorhídrico. La capa acuosa se se lavó con acetato de etilo, se basificó a pH 9 y se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida para dar 40 mg (40% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 225°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,55 (br s, 1H, NH), 8,51 (t, *J* = 5,5 Hz, 1H), 8,05 (br s, 1H, NH), 7,84 (d, *J* = 7,5 Hz, 1H), 7,79 (d, *J* = 8,0 Hz, 1H), 7,70 (d, *J* = 2,0 Hz, 1H), 7,59 (d, *J* = 2,0 Hz, 1H), 7,52 (t, *J* = 7,5 Hz, 1H), 7,18 (br s, 1H, NH), 3,39 (q, *J* = 6,5 Hz, 2H), 2,42 (t, *J* = 6,5 Hz, 2H), 2,19 (s, 6H), 1,89 - 1,78 (m, 6H), 1,65 (m, 1H), 1,54 (m, 2H), 1,31 (m, 1H).

Ejemplo 44

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-tiona

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=S, Y=NH

a) Preparación de 2',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (intermedio 1)

Una solución del Ejemplo 7 (51 mg, 2 mmol) en oxicloruro de fósforo (10 mL) que contiene Na_2CO_3 (32 mg, 3 mmol) se calentó a 95°C durante 5 horas. Después de enfriar a temperatura

ambiente, el oxicloruro de fósforo se removió bajo presión reducida. El producto crudo se usó sin purificación en el paso siguiente.

^{1}H NMR [$(CD_3)_2SO$] δ 8,31 (br s, 1H, NH), 7,28 (d, *J* = 7,8 Hz, 1H), 7,23 (d, *J* = 7,8 Hz, 1H), 7,04 (t, *J* = 7,8 Hz, 1H), 1,89-1,61 (m, 7H), 1,51-1,48 (m, 2H), 1,28-1,24 (m, 1H).

b) Preparación del Ejemplo 44

Una solución de 2',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (2 mmol) y tiourea (88 mg, 10,4 mmol) se calentó a reflujo toda la noche, se enfrió a temperatura ambiente y se concentró. El material se disolvió en EtOAc y se lavó secuencialmente con $NaHCO_3$ acuoso saturado NaCl acuoso saturado. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc :95/5) para dar el compuesto del título como un sólido blanco (288 mg, 54%). Punto de fusión= 209°C-211°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,15 (br s, 1H, NH), 8,69 (br s, 1H, NH), 7,39 (d, *J* = 7,9 Hz, 1H), 7,35 (d, *J* = 7,9 Hz, 1H), 7,09 (t, *J* = 7,9 Hz, 1H), 1,85 - 1,51 (m, 9H), 1,26 (m, 1H).

Ejemplo 45

8'-Cloro-2'-cianoiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina]

X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z^1=NH-CN, Y=N

2',8'-Dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (2 mmol) y cianamida (3 g) se calentó a 60°C toda la noche. La mezcla se enfrió a temperatura ambiente y se agregó agua. La solución acuosa se extrajo con CH_2Cl_2. Los extractos orgánicos se lavaron con NaCl acuoso saturado, se secaron sobre Na_2SO_4, se filtraron y se concentraron. Él material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc : 90/10) para dar el compuesto del título como un sólido blanco (260 mg, 23%). Punto de fusión = 193°C-195°C

^{1}H NMR [$(CD_3)_2SO$] δ 9,45 (br s, 1H, NH), 8,05 (br s, 1H, NH), 7,42 (d, *J* = 7,8 Hz, 1H), 7,37 (d, *J* = 7,8 Hz, 1H), 7,13 (t, *J* = 7,8 Hz, 1H), 1,81-1,57 (m, 9H), 1,28 (m, 1H).

Ejemplo 46

8'-Cloro-2'-metoxiiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolina]

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z^1= N-O-CH_3, Y= NH

Una solución de 2',8'-Dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (2 mmol) en EtOH (10 mL) se agregó a una solución de clorhidrato de metoxilamina (1 mg, 11,9 mmol) y trietilamina (1,67 mL, 11,9 mmol) en EtOH (3 mL) y se calentó a reflujo toda la noche, se enfrió a temperatura ambiente y se concentró. El material crudo se disolvió en EtOAc y se lavó secuencialmente con $NaHCO_3$ acuoso saturado y NaCl acuoso saturado. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc :80/20 a ciclohexano/EtOAc/MeOH : 80/20/1) para lograr el compuesto del título como un sólido blanco (120 mg, 22%). Punto de fusión = 113°C-115°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,17 (br s, 0.4H, NH), 7,64 (br s, 0,6H, NH), 7,33 (d, *J* = 8,0 Hz, 0,6H), 7,27 (d, *J* = 8,0 Hz, 0,6H), 7,25 (d, *J* = 7,5 Hz, 0,4H), 7,22 (d, *J* = 7,5 Hz, 0,4 H), 6,94 (t, *J* = 8,0 Hz, 0,6H), 6,87 (t, *J* = 7,5 Hz, 0,4H), 6,17 (br s, 0,6H, NH), 5,77 (br s, 0,4H, NH), 1,70 (m, 7H), 1,48 (m, 2H), 1,28 (m, 1H).

Ejemplo 47

8'-Cloro-2'-dimetilaminoespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolina]

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z^1= $N(CH_3)_2$, Y= N

Una solucion de 2',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (2 mmol) y dimetilamina (2M en etanol) (3mL, 6 mmol) se calentó a 140°C en un tubo sellado toda la noche, se enfrió a temperatura ambiente y se concentró. El material se disolvió en CH_2Cl_2 y se lavó secuencialmente con $NaHCO_3$ acuoso saturado y NaCl acuoso saturado. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc/NH_3 (28% en agua) :70/30/1) para lograr el compuesto del título como un sólido blanco (95 mg, 17%). Punto de fusión = 173°C-175°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,14 (d, *J* = 7,8 Hz, 1H), 7,04 (d, *J* = 7,8 Hz, 1H), 6,73 (t, *J* = 7,8 Hz, 1H), 5,84 (br s, 1H, NH), 3,0 (s, 6H), 1,73-1,53-(m, 9H), 1,29-1,17 (m, 1H).

Ejemplo 48

8'-Cloro-1'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= N-CH_3

A una solución agitada del Ejemplo 7 (150 mg, 0,59 mmol) en dimetilformamida (10 mL) se agregó hidruro de sodio (50% en grasa, 35,4 mg, 0,73 mmol) bajo N_2. La mezcla se se agitó hasta

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que cesó la evolución de hidrógeno y se agregó yoduro de metilo (40 µl, 0,65 mmol). La mezcla se agitó toda la noche bajo temperatura ambiente. Después de la remoción del solvente, el material se disolvió en CH_2Cl_2, se lavó con una solución acuosa saturada de NaCl, se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc 90/10) para lograr el compuesto del título como un sólido blanco (55 mg, 43%). Punto de fusión = 163°C-165°C

^{1}H NMR [$(CD_3)_2SO$] δ 7,34 (d, *J* = 7,8 Hz, 1H), 7,31 (d, *J* = 7,8 Hz, 1H), 7,08 (t, *J* = 7,8 Hz, 1H), 6,94 (br s, 1H, NH), 3,37 (s, 3H), 1,80-1,62 (m, 7H), 1,53 (m, 2H), 1,19 (m, 1H).

Ejemplo 49

8'-Cloro-1'-(etoxicarbonilmetil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= N-(etoxicarbonilmetilo)

Al Ejemplo 7 agitado (500 mg, 2 mmol) en dimetilformamida (10 mL) se agregó hidruro de sodio (50% en grasa, 96 mg, 2 mmol) bajo N_2. La mezcla se agitó toda la noche hasta que cesó la evolución de hidrógeno y se agregó bromoacetato de etilo (0,77 mL, 7 mmol). La mezcla se agitó toda la noche a 80°C. Después de la remoción del solvente bajo presión reducida, el material

se disolvió en CH_2Cl_2, se lavó con una solución acuosa saturada de NaCl, se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc/tolueno : 70/30/100) para lograr el compuesto del título como un sólido blanco (50 mg, 7%). Punto de fusión = 140°C-142°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,35 (d, *J* = 8,0 Hz, 1H), 7,32 (d, *J* = 8,0 Hz, 1H), 7,23 (br s, 1H, NH), 7,07 (t, *J* = 8,0 Hz, 1H), 4,71 (s, 2H), 4,09 (q, *J* = 7,5 Hz, 2H), 1,95-1,92 (m, 2H), 1,78-1,62 (m, 5H), 1,54-1,51 (m, 2H), 1,23 (m, 1H), 1,15 (t, *J* = 7,5 Hz, 3H).

Ejemplo 50

8'-Cloro-3'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= CH, X_3= CH, X_4= C-Cl, A= ciclohexilo, X= N-CH_3, Z= O, Y= NH

Preparación de 8'-Cloro-1'-(4-metoxibencil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (intermedio 2)

Una solución del Ejemplo 7 (5 g, 19,9 mmol), carbonato de cesio (7,8 g, 23,9 mmol) y cloruro de 4-metoxibencilo (2,9 mL, 21,93 mmol) en dimetilformamida (250 mL) se agitó a temperatura ambiente durante 3 días. La mezcla se concentró.

El residuo se disolvió en CH_2Cl_2, se lavó con una solución acuosa saturada de NaCl, se secó sobre Na_2SO_4, se filtró y se concentró. Se agregó AcOEt y el precipitado se filtró para lograr el compuesto del título como un sólido blanco (6,33 g, 86%).

^{1}H NMR [$(CD_3)_2SO$] δ 7,33 (d, *J* = 7,8 Hz , 1H), 7,26 (d, *J* = 7,8 Hz, 1H), 7,06 (m, 3H), 6,77 (d, *J* = 8,7 Hz, 2H), 5,25 (s, 2H), 3,66 (s, 3H), 1,67-1,47 (m, 5H), 1,40-1,27 (m, 4H), 1,13 (m, 1H).

Preparación de 8'-Cloro-3'-metil-1'-(4-metoxibencil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (intermedio 3)

A una solución agitada de 8'-cloro-1'-(4-metoxibencil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (260 mg, 0,7 mmol) en dimetilformamida (15 mL) se agregó hidruro de sodio (50% en grasa, 48 mg, 1 mmol) bajo N_2. La mezcla se agitó hasta que cesó la evolución de hidrógeno y se agregó yoduro de metilo (60 µl, 0,96 mmol). La mezcla se agitó toda la noche a temperatura ambiente. Después de la remoción del solvente, el material se disolvió en CH_2Cl_2, se lavó con NaCl acuos saturado, se secó sobre Na_2SO_4, se filtró y se concentró. El material crudo se purificó mediante cromatografía sobre gel de

sílice (ciclohexano/EtOAc/NH_2 acuoso al 28% :90/10/1) para el compuesto del título como un sólido blanco (190 mg, 70%).

^1H NMR [$(CD_3)_2SO$] δ 7,45 (d, *J* = 7,9 Hz, 1H), 7,40 (d, *J* = 7,9 Hz, 1H), 7,12 (t, *J* = 7,9 Hz, 1H), 7,07 (d, *J* = 8,2 Hz, 2H), 6,79 (d, *J* = 8,2 Hz, 2H), 5,25 (s, 2H), 3,67 (s, 3H), 2,85 (s, 3H), 1,66-1,35 (m, 10H).

Preparación del Ejemplo 50

A una solución de 8'-Cloro-3'-metil-1'-(4-metoxibencil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (180 mg, 047 mmol) en CH_2Cl_2 (4 mL) enfriada a -10°C se agregó gota a gota ácido trifluoroacético (4 mL). La mezcla se agitó a -10°C durante 1 hora y a temperatura ambiente durante 20 min. La mezcla se vertió en una solución acuosa saturada de $NaHCO_3$ y se extrajo con CH_2Cl_2. Los extractos orgánicos se lavaron con una solución acuosa saturada de NaCl, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc/NH_3 (28% en agua) :90/10/1 a 70/30/1) para lograr el compuesto del título como un sólido blanco (21 mg, 17%). Punto de fusión = 135-137°

^{1}H NMR [$(CD_3)_2SO$] δ 8,80 (br s, 1H, NH), 7,46 (d, *J* = 7,7 Hz, 1H), 7,29 (d, *J* = 7,7 Hz, 1H), 7,00 (t, *J* = 7,7 Hz, 1H), 2,96 (s, 3H), 1,96 (m, 4H), 1,66 (m, 2H), 1,56-1,39 (m, 4H).

Ejemplo 51

8'-Cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= C-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenilo], X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= NH

A una suspensión del Ejemplo 32 (185 mg, 0,5 mmol) en tolueno (10 mL) se agregó cloruro de tionilo (0,19 mL, 1,9 mmol, 5 equiv.). La mezcla resultante se calentó a reflujo durante 2 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (4 mL) se agregó trietilamina (0,15 mL, 1 mmol, 2 equiv.) y 2-(1-piperazinil)pirimidina (100 mg, 0,6 mmol, 1.2 equiv.). Después de calentar a 80°C durante 1 h, la mezcla se diluyó con diclorometano y se lavó con agua. La capa orgánica se concentró bajo presión reducida y el sólido resultante se purificó mediante cromatografía sobre gel de sílice (CH_2Cl_2/MeOH : 97/3) para dar 210 mg (81% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 271°C

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^{1}H NMR [$(CD_3)_2SO$] δ 8,30 (br s, 1H, NH), 8,15 (d, *J* = 4,5 Hz, 2H), 7,55 (d, *J* = 8,0 Hz, 2H), 7,44 (s, 1H), 7,39 (s, 1H), 7,27 (d, *J* = 8,5 Hz, 2H), 6,94 (br s, 1H, NH), 6,43 (t, *J* = 4,5 Hz, 1H), 3,57-3,27 (m, 8H), 1,69 - 1,54 (m, 6H), 1,41 (m, 1H), 1,30 (m, 2H), 1,07 (m, 1H).

Ejemplo 52

8'-Cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= C-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenilo], X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= NH

A una suspensión del Ejemplo 32 (150 mg, 0,4 mmol) en tolueno (2 mL) se agregó cloruro de tionilo (0,06 mL, 0,8 mmol, 2 equiv.). La mezcla resultante se calentó a reflujo durante 2 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (2 mL) se agregó trietilamina (0,11 mL, 0,8 mmol, 2 equiv.) y 1-[2-(morfolin-4-il)-etil]-piperazina (64 mg, 0,3 mmol, 0,8 equiv.). Después de agitar durante 2 h, la mezcla se diluyó con diclorometano, se lavó con agua y con una solución acuosa a 1M de hidróxido de sodio. La capa orgánica se secó sobre sulfato de sodio, se concentró bajo presión reducida y el sólido resultante se trituró con acetato

de etilo/metanol para dar 106 mg (50% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 264°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,53 (br s, 1H, NH), 7,75 (m, 2H), 7,65 (s, 1H), 7,60 (s, 1H), 7,43 (m, 2H), 7,17 (br s, 1H, NH), 3,53 (m, 8H), 2,50-2,36 (m, 12H), 1,84 - 1,78 (m, 6H), 1,63 (m, 1H), 1,56 (m, 2H), 1,29 (m, 1H).

Ejemplo 53

8'-Cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= C-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenilo], X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= NH

A una suspensión del Ejemplo 32 (150 mg, 0,4 mmol) en tolueno (2 mL) se agregó cloruro de tionilo (0,06 mL, 0,8 mmol, 2 equiv.). La mezcla resultante se calentó a reflujo durante 3 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (2 mL) se agregó trietilamina (0,11 mL, 0,8 mmol, 2 equiv.) y 4-[2-(piperazin-1-il)-acetil]-morfolina (130 mg, 0,6 mmol, 1,5 equiv.). Después de agitar toda la noche, la mezcla se diluyó con diclorometano, se lavó con agua y con una solución acuosa saturada de bicarbonato de sodio. La

capa orgánica se secó sobre sulfato de sodio, se concentró bajo presión reducida y el sólido resultante se trituró con acetato de etilo/metanol para dar 0,1 g (45% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión =239 °C

^{1}H NMR [$(CD_3)_2SO$] δ 8,53 (br s, 1H, NH), 7,74 (d, *J* = 8,0 Hz, 2H), 7,66 (s, 1H), 7,60 (s, 1H), 7,44 (d, *J* = 8,0 Hz, 2H), 7,17 (br s, 1H, NH), 3,58-3,22 (m, 14H), 2,50 (m, 4H), 1,88 - 1,79 (m, 6H), 1,64 (m, 1H), 1,55 (m, 2H), 1,30 (m, 1H).

Ejemplo 54

8'-Cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1= CH, X_2= C-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenilo], X_3= CH, X_4= C-Cl, A= ciclohexilo, X= NH, Z= O, Y= NH

A una suspensión del Ejemplo 32 (150 mg, 0,4 mmol) en tolueno (2 mL) se agregó cloruro de tionilo (0,06 mL, 0,8 mmol, 2 equiv.). La mezcla resultante se calentó a reflujo durante 3 h, luego se concentró bajo presión reducida. Al sólido resultante en tolueno (2 mL) se agregó trietilamina (0,11 mL, 0,8 mmol, 2 equiv.) y 1-hidroxietiletoxipiperazina (77 mg, 0,4 mmol, 1,1 equiv.). Después de agitar a 2 h, la mezcla se

diluyó con diclorometano y se lavó con agua y con una solución acuosa a 1M de hidróxido de sodio. La capa orgánica se secó sobre sulfato de sodio, se concentró bajo presión reducida para dar 0,06 g (29% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión =100°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,53 (br s, 1H, NH), 7,75 (d, *J* = 8,0 Hz, 2H), 7,65 (s, 1H), 7,60 (s, 1H), 7,43 (d, *J* = 8,0 Hz, 2H), 7,17 (br s, 1H, NH), 4,58 (br s, 1H), 3,59-3,39 (m, 10H), 2,45 (m, 6H), 1,88 - 1,77 (m, 6H), 1,64 (m, 1H), 1,54 (m, 2H), 1,30 (m, 1H).

Ejemplo 55

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-imidazo[2,1-b]quinazolina

fórmula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X-Z=NCH=CHNH, Y=NH

Preparación de 8'-Cloro-2'-(2,2-dimetoxi-etilamino)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina] (intermedio 4)

Una solución del Ejemplo 7 (1,34 mmol, 0,5 g) en oxicloruro de fósforo (7 mL) que contiene Na_2CO_3 (21 mg, 2 mmol) se calienta a 95°C durante 4 horas. Después de enfriar a temperatura ambiente, el oxicloruro de fósforo se removió bajo presión

reducida. El residuo se tomó en EtOH (10 mL), se agregó amino acetaldehído dimetil acetal (1 mL, 8,04 mmol) y la mezcla resultante se refluyó toda la noche. Se agregó CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron tres veces con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/ EtOAc/ MeOH: 80/20/5) para dar 0,43 g (96%) del intermedio 4.

^1H NMR [$(CD_3)_2SO$] δ 7,12 (d, J = 7,5 Hz, 1H), 7,04 (d, J = 7,5 Hz, 1H), 6,70 (t, J = 7,5 Hz, 1H), 6,46 (br s, 1H), 6,08 (br s, 1H), 4,48 (t, J = 5,3 Hz, 1H), 3,41 (t, J = 5,3 Hz, 2H), 3,32 (m, 6H), 1,72-1,56 (m, 9H), 1,22 (m, 1H).

Preparación del Ejemplo 55

Una solución del intermedio 4 (0,436 g, 1,29 mmol) en una mezcla de alcohol isopropílico (10 mL) y HCl acuoso 3M (4 mL) se refluyó toda la noche. La mezcla de la reacción se dejó enfriar a temperatura ambiente, se concentró bajo presión reducida y se tomó en CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El

material crudo se recristalizó en EtOAc para lograr el compuesto del título como un sólido blanco (0,07 g, 23%) (pureza = 95,4%) Punto de fusión = 197°C-199°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,58 (br s, 1H), 7,52 (m, 1H), 7,34 (d, *J* = 7,7 Hz, 1H), 7,23 (d, *J* = 1,5 Hz, 1H), 6,92 (t, *J* = 7,7 Hz, 1H), 6,71 (d, *J* = 1,5 Hz, 1H), 2,03 (m, 4H), 1,37-1,45 (m, 6H).

Ejemplo 56

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-[1,2,4]triazolo[3,4-b]quinazolina

fórmula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X-Z: NCH=NN, Y=NH

Preparación de 8'-Cloroespiro[ciclohexana-1-4'-(3',4'-dihidro)-quinazolin-2'-yl]-hidrazina

Una solución del Ejemplo 7 (1,8 mmol, 0,45 g) en oxicloruro de fósforo (9 mL) que contiene Na_2CO_3 (0,28 g, 2,7 mmol) se calienta a 95°C durante 4 horas. Después de enfriar a temperatura ambiente, el oxicloruro de fósforo se removió bajo presión reducida. El residuo se tomó en EtOH (10 mL), hidrazina (35% en peso de solución en agua, 2 mL) se agregó y la mezcla resultante se refluyó toda la noche. Se agregó CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las

capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El material crudo (0,43 g, 91%) se usó sin nueva purificación en el paso siguiente. 1H NMR [$(CD_3)_2SO$] δ 7,12 (d, 1H), 7,08 (m, 1H), 6,75 (t, 1H), 1,83-1,60 (m, 7H), 1,47 (m, 2H), 1,25 (m, 1H).

Preparación del Ejemplo 56

Una solución de 8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin-2'-il]-hidrazina (0,58 g, 2,19 mmol), trietil ortoformato (1,82 mL, 10,95 mmol) y H_2SO_4 (0,05 mL) en butanol (20 mL) se refluyó durante 24 h. La mezcla de la reacción se dejó enfriar a temperatura ambiente, se concentró bajo presión reducida y se tomó en una mezcla de CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El material crudo se recristalizó en EtOAc para lograr el compuesto del título como un sólido blanco (0,13 g, 21%).

(pureza = 96,6%) Punto de fusión = 237-239°C.

^1H NMR [$(CD_3)_2SO$] δ 9,99 (br s, 1H), 8,72 (s, 1H), 7,55 (dd, J = 7,9, 1,0 Hz, 1H), 7,37 (dd, J = 7,9, 1,0 Hz, 1H), 6,97 (t, J = 7,9 Hz, 1H), 2,07 (m, 4H), 1,72 (m, 5H), 1,53 (m, 1H).

Ejemplo 57

9'-Cloroespiro[ciclohexano-1-5'-(4',5'-dihidro)]-[1,2,4]triazolo[4,3-a]quinazolina

fórmula (I), X_1=CH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Y-Z: NCH=NN

A una solución de 8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin-2'-il]-hidrazina (0,35 g, 1,32 mmol) y trietil ortoformato (1,2 mL, 7,22 mmol) en $CHCl_3$ (16 mL) se agregó H_2SO_4 (0,04 mL). La mezcla se agitó a temperatura ambiente durante 3 h, se concentró bajo presión reducida y se tomó en una mezcla de CH_2Cl_2 y una solución saturada acuosa de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El residuo se tomó en butanol (10 mL) y se refluyó toda la noche. Después de completarlo, el solvente se evaporó bajo presión reducida para dar una mezcla de 9'-Cloroespiro[ciclohexano-1-5'-(4',5'-dihidro)]-[1,2,4]triazolo[4,3-a]quinazolina y 9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-[1,2,4]triazolo[3,4-b]quinazolina a razón de 88/12. La cristalización en CH_2Cl_2 dio el compuesto del título como un polvo blanco (0,045 g, 43%).

(pureza = 97,2%) Punto de fusión = 285°C-287°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,14 (s, 1H), 7,55 (m, 2H), 7,46 (s, 1H), 7,35 (t, *J* = 8,0 Hz, 1H), 1,85-1,64 (m, 7H), 1,50 (m, 2H), 1,23 (m, 1H).

Ejemplo 58

Espiro[ciclohexano-1-9'-(8',9'-dihidro)-pirazolo[4',3'-*f*]quinazolin]-7'(6'H)-ona

Fórmula (I): X_1-X_2=C-CH :NNH-C, X_3=CH, X_4=CH, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo A usando (N-(1H-indazol-5-il)urea (1 g, 5,67 mmol), ácido polifosfórico (20 g) y ciclohexanona (0,9 mL, 1,5 equiv.). El producto crudo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/01 a 97/3) seguido por la recristalización en tolueno para dar el compuesto del título como un sólido blanco (14 mg, 1% de rendimiento) (pureza 98,8%).

^{1}H NMR [$(CD_3)_2SO$] δ 12,97 (br s, 1H, NH), 8,98 (br s, 1H, NH), 8,16 (s, 1H), 7,33 (d, *J* = 8,5 Hz, 1H), 6,88 (d, *J* = 9,0 Hz, 1H), 6,70 (br s, 1H, NH), 2,33-2,20 (m, 2H), 1,89-1,78 (m, 4H), 1,68-1,41 (m, 4H).

Ejemplo 59

8'-Cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de (2-Cloro-5-metoxi-fenil)-urea (intermedio 5)

Una solución de 2-cloro-5-metoxianilina (5 g, 25,76 mmol) y cianato de potasio (5,22 g, 64,41 mmol) en una mezcla de ácido acético (125 mL) y agua (12,5 mL) se agitó a temperatura ambiente. El solvente se evaporó, y el residuo se tomó en una mezcla de CH_2Cl_2 y una solución acuosa saturada de $NaHCO_3$. Las capas se separaron, la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El material crudo se purificó mediante cromatografía rápida sobre gel de sílice (ciclohexano/ EtOAc/ MeOH: 80/20/2) para dar 2,06 g (40%) del intermedio 5.

^{1}H NMR [$(CD_3)_2SO$] δ 7.97 (br s, 1H, NH), 7,85 (d, *J* = 3,0 Hz, 1H), 7,27 (d, *J* = 9,0 Hz, 1H), 6,54 (dd, *J* = 9,0, 3,0 Hz, 1H), 6,4 (br s, 2H), 3,71 (s, 3H).

Preparación del Ejemplo 59

El Ejemplo 59 se preparó de acuerdo con el protocolo A usando el intermedio 5 (1 g, 4,98 mmol), ácido polifosfórico (15 g) y

ciclohexanona (0,88 mL, 7,47 mmol). Después completar, se agregó hielo, el precipitado se filtró y se lavó con agua fría. El residuo se recristalizó en etanol para lograr el compuesto del título como un polvo blanco (0,6 g, 78% de rendimiento) (pureza 99,54%) Punto de fusión = 228,5°C-230.5°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,93 (br s, 1H, NH), 7,27 (d, *J* = 8,9 Hz, 1H), 7,00 (br s, 1H, NH), 6,65 (d, *J* = 8,9 Hz, 1H), 3,79 (s, 3H), 2,45-2,38 (m, 2H), 1,84-1,74 (m, 2H), 1,63-1,56 (m, 3H), 1,46 (m, 2H), 1,23-1,13 (m, 1H).

Ejemplo 60

5',8'-Difluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-F, X_2=CH, X_3=CH, X_4=C-F, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de 2,5-difluorofenil urea (intermedio 6)

A una solución de isocianato de 2,5-difluorofenilo (1 g, 6,45 mmol) en tetrahidrofurano (50 mL) a 0°C se agregó una solución acuosa al 28% de amoníaco (30 mL). La mezcla se agitó durante 1h permitiendo que la temperatura se calentara a temperatura ambiente, luego se concentró bajo presión reducida, se tomó en gua y se filtró. El sólido se lavó dos veces con agua y con

éter, luego se secó a 65°C bajo presión reducida para dar 740 mg (67%) del intermedio 6.

^{1}H NMR [$(CD_3)_2SO$] δ 8,53 (br s, 1H, NH), 8,02 (m, 1H), 7,21 (m, 1H), 6,72 (m, 1H), 6,29 (br s, 2H, NH_2).

Preparación del Ejemplo 60

El compuesto del título se preparó de acuerdo con el protocolo A usando el intermedio 6 (740 mg, 4,3 mmol), ácido polifosfórico (20 g) y ciclohexanona (0,70 mL, 6,75 mmol). El producto crudo se purificó mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 100/0 a 95/5) seguido por la cristalización en tolueno para dar el compuesto del título como un sólido blanco (28 mg, 3% de rendimiento) (pureza 99%)
Punto de fusión = 194°C-195°C.

^{1}H NMR [$(CD_3)_2SO$] δ 9,26 (br s, 1H, NH), 7,13 (m, 1H), 7,05 (br s, 1H, NH), 6,71 (m, 1H), 2,01 (m, 2H), 1,86-1,75 (m, 4H), 1,64 (m, 1H), 1,49 (m, 2H), 1,18 (m, 1H).

Ejemplo 61

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-CH_3, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=C, Y=NH

Preparación de (2-cloro-5-metil-fenil)urea (intermedio 7)

Una solución de 2-cloro-5-metilanilina (10 g, 70,6 mmol) y cianato de potasio (14,3 g, 176 mmol) en una mezcla de ácido acético (340 mL) y agua (34 mL) se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó y el residuo se recogió en una mezcla de CH_2Cl_2 una solución saturada acuosa de $NaHCO_3$. El precipitado se filtró, se lavó con diclorometano y se secó bajo vacío para dar 12,6 g (97%) del intermedio 7. ^1H NMR [$(CD_3)_2SO$] δ 8,05 (s, 1H, NH), 7,96 (s, 1H), 7,23 (d, 1H), 6,75 (d, 1H), 6,37 (br s, 2H), 2,24 (s, 3H).

Preparación del Ejemplo 61

El compuesto del título se preparó de acuerdo con el protocolo A usando el intermedio 7 (12,6 g, 68,2 mmol), ácido polifosfórico (150 g) y ciclohexanona (8,5 mL, 81,9 mmol). Después de completar, la mezcla se vertió en hielo y agua y se agitó durante 45 minutos. El precipitado se filtró y se lavó con agua fría, con éter dietílico y se secbó bajo vacío para dar 3,1 g del compuesto del título. El residuo (100mg) se recristalizó en etanol para dar el compuesto del título como un polvo blanco (0,06 g, 17% de rendimiento) (pureza con HPLC: 99,9%).

^{1}H NMR [$(CD_3)_2SO$] δ 8,02 (br s, 1H, NH), 7,20 (d, J = 8,04 Hz, 1H), 6,89 (br s, 1H, NH), 6,57 (d, J = 8,03 Hz, 1H), 2,47 (s, 3H), 2,02-2,18 (m, 2H), 1,70-1,90 (m, 4H), 1,62-1,70(m, 1H), 1,48-1,60 (m, 2H), 1,20-1,35 (m, 1H).

Ejemplo 62

8'-Cloro-6'-(morfolin-4-il)metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-CH_2-morfolinilo, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se perparó de acuerdo con el protocolo E. A una solución agitada del Ejemplo 7 (1 g, 4 mmol) en ácido acético glacial (15 mL) se agregó secuentialmente trioxano (0,55 g, 6 mmol, 1,5 equiv.) y una solución acuosa al 48% de ácido bromhídrico (5 mL). La mezcla se calentó a 95°C toda la noche, se vertió sobre hielo. El precipitado se filtró, se lavó dos veces con agua y luego con éter para dar 1,39 g de 8'-Cloro-6'-bromometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona como un sólido blanco. El derivado de bromometilo crudo (150 mg, 0,43 mmol) fue tratado con morfolina (0,100 mL, 1,1 mmol, 2,6 equiv.) en DMF (3 mL) toda la noche. La mezcla se concentró bajo presión reducida, se tomó en acetato de etilo, se extrajo con HCl acuoso 1N. La capa acuosa se lavó dos veces con acetato de etilo, se

basificó a pH 9 y se extrajo tres veces con acetato de etilo. Las capas orgánicas combinadas se lavaron tres veces con agua y solución salina y se concentraron bajo presión reducida. El material crudo se purificó por cristalización en tolueno para dar el compuesto del título (102 mg, 68%) (pureza 97%) como un sólido blanco. Punto de fusión = 223°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,33 (br s, 1H, NH), 7,21 (s, 1H), 7,18 (s, 1H), 7,08 (br s, 1H, NH), 3,56 (m, 4H), 3,39 (s, 2H), 2,32 (m, 4H), 1,84-1,49 (m, 9H), 1,25 (m, 1H).

Ejemplo 63

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OH, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 59 (0,83 g, 2,95 mmol) en CH_2Cl_2 (100 mL) se agregó tribromuro de boro (1 N en CH_2Cl_2, 21,8 mL, 21,8 mmol) a 0°C. La mezcla se agitó a temperatura ambiente durante 48 h, se vertió en una solución saturada acuosa de $NaHCO_3$ y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se

purificó mediante precipitación en Et_2O para lograr el compuesto del título como un sólido blanco (0,25 g, 32%). (pureza 97,6%) Punto de fusión = 252-254°C.

^1H NMR [$(CD_3)_2SO$] δ 9,90 (br s, 1H), 7,75 (br s, 1H), 7,08 (d, *J* = 8,7 Hz, 1H), 6,97 (br s, 1H, NH), 6,43 (d, *J* = 8,7 Hz, 1H), 2,58-2,54 (m, 2H), 1,83-1,72 (m, 2H), 1,62-1,53 (m, 3H), 1,46 (m, 2H), 1,24-1,07 (m, 1H).

Ejemplo 64

8'-Cloro-5'-hidroxi-6'-yodo-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-OH, X_2=C-I, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión agitada del Ejemplo 63 (10 g, 37,5 mmol) en ácido trifluoroacético (150 mL) de 0°C a 5°C se agregó N-yodosuccinimida (9,47 g, 41,2 mmol) en porciones durante 10 minutos. La mezcla de la reacción se agitó de 0°C a 5°C durante 2 horas. La mezcla se vertió sobre una mezcla de agua (700 mL) y hielo (300 mL). El sólido marrón resultante se filtró y se lavó con agua (250 mL) y luego heptano (4 x 40 mL). El sólido se tiró seco sobre el lecho del filtro durante 2 horas y luego se suspendió en una mezcla de diclorometano (30 mL) y metanol (5 mL). El precipitado roza oscuro se filtró y se lavó con

diclorometano (3 x 20mL) para lograr el compuesto del título (12,2 g, 31,0 mmol, 83%).

^{1}H NMR [$(CD_3)_2SO$] δ 9,10 (s, 1H), 8,25 (s, 1H), 7,81 (s, 1H), 7,18 (s, 1H), 2,70 (m, 2H), 1,95 (m, 2H), 1,75 (m, 3H), 1,60 (m, 2H), 1,28 (m, 1H).

Ejemplo 65

8'-Cloro-6'-yodo-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=C-I, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión agitada del Ejemplo 64 (16,27 g, 41,4 mmol) en DMF (325 mL) se agregó DBU (7,5 mL, 50,1 mmol) y luego yoduro de metilo (6,8 mL, 109 mmol) de 20°C a 25°C. La mezcla de la reacción se agitó durante 3 horas. La mezcla se vartió en agua (1625 mL) y el sólido resultante se filtró y se lavó con agua (500 mL) y luego heptano (2 x 150 mL). El sólido se agitó en acetato de etilo que contenía metanol al 10% (100 mL) durante 10 minutos. El precipitado se filtró y se lavó con EtOAc (25 mL), TBME (10 mL) y se secó *en vacío* a 50°C para lograr el compuesto del título como un sólido de color cervato (14,4 g, 35,5 mmol, 86%).

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^{1}H NMR [$CDCl_3$] δ 7,67 (s, 1H), 7,18 (s, 1H), 5,68 (s, 1H), 3,83 (s, 3H), 2,23 (td, J = 13,6, 4,5, 2H), 1,90 (m, 2H), 1,70 (m, 3H), 1,51 (m, 2H), 1,25 (m, 1H).

Ejemplo 66

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=C-CN, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 65 (3g, 7,38 mmol) en NMP (60 mL) de 18°C a 20°C se agregó cianuro de cobre (I) (555 mg, 6,2 mmol). La mezcla se calento a 150°C durante 4 días, se enfrió en hielo/agua (300 mL) y el producto crudo se filtró. El producto crudo se disolvió en EtOAc (500mL) y se lavó con una solución de NH_3(ac) al 33% (2 x 200 mL). La capa orgánica se lavó nuevamente con solución salina (2x 100mL) y agua (2x 100mL) y se secó sobre $MgSO_4$, se filtró y se concentró *en vacío* a 40°C para dar el producto crudo (1,2g, 3,92 mmol). El producto crudo (650mg, 2,12 mmol) se purificó mediante HPLC preparativa para dar el compuesto del título como un sólido amarillo pálido (97mg, 3,27mmol, 4%) (pureza 96%).

^{1}H NMR (360MHz, d^6-DMSO) δ 1,29-1,43 (m, 1H), 1,50-1,70 (m, 2H), 1,73-1,95 (m, 5H), 2,25 (ddd, *J* = 4,5, 13,5 & 13,5Hz,

2H), 4,17 (s, 3H), 5,62-5,68 (br s, 1H), 7,25-7,29 (br s, 1H), 7,54 (s, 1H).

Ejemplo 67

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2CH_2-(4-morfolinilo), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (1 g, 3,93 mmol) en DMF (30 mL) bajo nitrógeno de 18°C a 20°C se agregó una dispersión de hidruro de sodio al 60% (0,16 g, 3,93 mmol). La mezcla se agitó durante 15 minutos antes de agregar 4-(2-cloroetil)morfolina (0,59 g, 3,93 mmol). La mezcla luego se calentó a 100°C durante 1,5 horas. Después de enfriar a temperatura ambiente la mezcla de la reacción se agregó a agua (300 mL). El sólido resultante se filtró y se lavó con agua (50 mL). El sólido crudo se secó en vacío a 45°C y la posterior purificación mediante cromatografía de columna (sílice 60 g, eluyendo con metanol al 5% en diclorometano) dio el compuesto del título (0,48 g, 1,23 mmol, 32%) como un sólido color crema después de secar en vacío a 50°C.

(pureza 96,9%)

^{1}H NMR (360 MHz, $CDCl_3$) δ 7,20 (d, *J* = 8,8 Hz, 1H), 7,04 (s, 1H), 6,50 (d, *J* = 8,8 Hz, 1H), 5,65 (s, 1H), 4,10 (t, *J* = 5,5 Hz, 2H), 3,73 (t, *J* = 4,5 Hz, 4H), 2,84 (t, *J* = 5,5 Hz, 2H), 2,68 (td, *J* = 13,5, 4,5 Hz, 2H), 2,56 (t, *J* = 4,5 Hz, 4H), 1,74 (m, 5H), 1,56 (m, 2H), 1,32 (m, 1H).

Ejemplo 68

8'-Cloro-5'-[2-dimetilaminoetoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 63 (6g, 22,5mmol) en DMF (20mL) de 18°C a 20°C se agregó a una solución de carbonato de potasio (2M, 9,42mL, 18,84mmol) y luego cloruro clorhidrato de de 2-dimetil-aminoetilo (2M, 37,7mL, 75,4mmol). La mezcla se calentó a 100°C durante 18 horas y se dejó enfriar de 18°C a 20°C. La mezcla de la reacción se agregó a agua (1,5L) y se extrajo con EtOAc (2x1L). La capa orgánica combinada se lavó nuevamente con agua (1L) y se separó. Las fracciones orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron *en vacío* a 40°C para dar el material crudo (4,7g, 13,9mmol). El producto crudo se purificó mediante el lavado con TBME (60 ml) y el tratamiento con carbón vegetal (5g) en

DCM (200mL) y cromatografía de columna (sílice; gradiente de elución, 100% EtOAc a 50% en DCM a EtOAc:DCM:MeOH; 2:10:1) para dar el compuesto del título como un sólido amarillo pálido (2,34g, 6,93mmol, 31%) (pureza 99%)

^{1}H NMR (360MHz, d^6-DMSO) δ 1,21-1,33 (m, 1H), 1,40-1,55 (m, 2H), 1,60-1,72 (m, 5H), 2,29 (s, 6H), 2,57 (ddd, *J* = 4,5, 13,5, 13,5 Hz, 2H), 2,72 (t, *J* = 6,1 Hz, 2H), 4,02 (t, *J* = 6,1 Hz, 2H), 5,48-5,54 (br s, 1H), 6,45 (d, *J* = 9,0 Hz, 1H), 6,92-6,97 (br s, 1H), 7,14 (d, *J* = 9,0 Hz, 1H);

Ejemplo 69

8'-Cloro-5'-(2-aminoetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2NH_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de 8'-Cloro-5'-(2-metanosulfoniletoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (intermedio 8)

A una solución agitada del Ejemplo 78 (5 g, 1,61 mmol) y trietilamina (1,95 g, 1,93 mmol) en diclorometano (200 mL) de 0°C a 5°C se agregó una solución de cloruro de metanosulfonilo (2,21 g, 1,93 mmol) en diclorometano (10 mL). La mezcla de la reacción se agitó de 20°C a 25°C durante 5 horas. La mezcla se

lavó con agua (2 x 100 mL) y la fase orgánica se secó sobre sulfato de magnesio. La filtración y la concentración en vacío a 40°C dieron el intermedio 8 como un sólido blancuzco (5,4 g, 1,39 mmol, 86%).

^{1}H NMR [$CDCl_3$] δ 7,13 (d, J = 9,1 Hz, 1H), 6,99 (s, 1H), 6,38 (d, J = 9,1 Hz, 1H), 5,60 (s, 1H), 4,53 (m, 2H), 4,20 (m, 2H), 3,00 (s, 3H), 2,47 (td, J = 13,6, 4,5 Hz, 2H), 1,59 - 1,78 (m, 5H), 1,48 (m, 2H), 1,28 (m, 1H).

Preparación del Ejemplo 69

El Intermedio 8 (1,0 g, 2,57 mmol) se agitó con una solución de amoníaco en etanol (40 mL) a 70°C en un recipiente a presión sellado durante 21 horas. El etanol se removió mediante evaporación *en vacío* a 40°C para dejar un residuo sólido de color cervato (0,81 g). Se agregó 2N-ácido clorhídrico (40 mL) (no ocurrió disolución), la suspensión acuosa ácida se trató con 2N-hidróxido de sodio a pH 12. La mezcla acuosa se extrajo dos veces con acetato de etilo que contenía metanol al 10% (45 mL yd 80 mL). El acetato de etilo combinado se lavó una vez con agua (50 mL), se secó sobre sulfato de magnesio, se filtró y se concentrí *en vacío* a 40°C a un volumen bajo (10 mL). Un sólido blancuzco se filtró y se lavó con acetato de etilo (5 mL). La amina cruda se purificó mediante cromatografía de columna (sílice 20 g, eluyendo con 20% metanol en

diclorometano) para dar el compuesto del título como un sólido blancuzco después de secar *en vacío* a 50°C (0,30 g, 0,97 mmol, 38%) (pureza 98,7%).

^{1}H NMR [$(CD_3)_2SO$] δ 7,80 (br s, 1H), 7,10 (d, J = 8,8 Hz, 1H), 6,90 (s, 1H), 6,48 (d, J = 8,8 Hz, 1H), 3,78 (t, J = 5,6, 2H), 2,78 (t, J = 5,6, 2H), 2,40 (m, 2H), 1,65 (m, 2H), 1,25 a 1,51 (m, 7H), 1,01 (m, 1H);

Ejemplo 70

8'-Cloro-5'-[2-(metilamino)etoxi]-espiro[ciclohexane-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2NHCH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El Intermedio 8 (0,4 g, 1,03 mmol) se agitó con una solución de metilamina en etanol (27 mL) a 70°C durante 7 horas. El etanol se removió mediante evaporación *en vacío* a 40°C y el residuo se particionó entre agua (25 mL) y acetato de etilo (50 mL), agregando 2M-hidróxido de sodio (2 mL) para garantizar que el pH fuera ≥ 12. El acetato de etilo se lavó una vez con agua (15 mL), se secó sobre sulfato de magnesio y se concentró *en vacío* a 40°C para dar un residuo sólido roza. La amina cruda se purificó mediante cromatografía de columna (sílice 20 g, eluyendo con 4% trietilamina y 16% metanol en

acetato de etilo) para dar el compuesto del título (0,23 g, 0,71 mmol, 69%) como un sólido blancuzco después de secar *en vacío* a 50°C. (pureza 99%)

^{1}H NMR (d_6 DMSO) δ 1,21 (m, 1H), 1,54 (m, 2H), 1,68 (m, 3H), 1,85 (m, 2H), 2,41 (s, 3H), 2,58 (m, 2H), 2,95 (t, *J* = 5,7Hz, 2H), 4,08 (t, *J* = 5,7Hz, 2H), 6,70 (d, *J* = 8,9Hz, 1H), 7,12 (s, 1H), 7,31 (d, *J* = 8,9Hz, 1H), 8,02 (s, 1H).

Ejemplo 71

8'-Cloro-5'-[2-(2-aminoetoxi)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2OCH_2CH_2NH_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 63 (1,07 g, 4,0 mmol) en DMF (20 mL) a temperatura ambiente se agregó carbonato de potasio (1,22 g, 8,8 mmol) y 2-[2-(2-cloroetoxi)etil]-1H-isoindol-1,3(2H)-diona (1,22 g, 4,8 mmol). La mezcla se calentó a 100°C durante 8 horas. Se agregaron más carbonato de potasio (1,22 g) y 2-[2-(2-cloroetoxi)etil]-1H-isoindol-1,3(2H)-diona (1,22 g) y la mezcla se agitó a 100°C durante otras 9 horas. Después de enfriar de 18°C a 20°C la mezcla de la reacción se agregó a agua (200 mL). El sólido resultante se filtró y se lavó con agua (50 mL). El sólido se purificó

mediante cromatografía de columna (sílice 50 g, eluyendo con 5% metanol en diclorometano) para dar el intermedio ftalimida (1,0 g, 2,06 mmol, 52%) como un sólido vítreo rosa. A una suspensión agitada del intermedio ftalimida (0,9 g, 1,86 mmol) en etanol (23 mL) se agregó hidrazina hidratada (0,28 mL, 5,64 mmol). La mezcla se calentó a 60°C durante 4 horas. Se agregó 2M-ácido clorhídrico (36 mL) y la reacción se calentó a reflujo durante 1,25 horas. El enfriamiento de 18°C a 20°C dio un sólido que se aisló mediante filtración y se lavó con agua (10 mL). El pH del filtrado se ajustó a 14 agregando 2M-hidróxido de sodio (2 mL), la amina cruda se precipitó y se filtró y lavó con agua (10 mL) y TBME (10 mL). La amina se purificó mediante cromatografía de columna (sílice 20 g, eluyendo con 4% trietilamina y 16% metanol en acetato de etilo) para dar el compuesto del título (0,43 g, 1,21 mmol, 65%) como un compuesto sólido después de secar *en vacío* a 50°C. (pureza 98%)

^{1}H NMR (360 MHz, d_6 DMSO) δ 1,40 (m, 1H), 1,65 (m, 2H), 1,75 (m, 3H), 2,00 (m, 2H), 2,77 (m, 2H), 2,87 (t, J = 5,9Hz, 2H), 3,65 (t, J = 5,9Hz, 2H), 3,95 (m, 2H), 4,29 (m, 2H), 6,81 (d, J = 9,0Hz, 1H), 7,22 (s, 1H), 7,44 (d, J = 9,0Hz, 1H), 8,13 (s, 1H).

Ejemplo 72

8'-Cloro-5'-[3-dimetilaminopropoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 63 (1,5g, 5,63mmol) en DMF (20mL) de 18°C a 20°C se agregó una solución de carbonato de potasio (2M, 9,42mL, 18,84mmol) y luego clorhidrato de cloruro de 3-dimetil-aminopropilo (1,02g, 6,45mmol). La mezcla se calentó a 100°C durante 18 h. Luego se agregó a agua (400mL) y se extrajo con EtOAc (2x400mL). La capa orgánica combinada se lavó nuevamente con agua (300mL) y se separó. Se secó con $MgSO_4$, se concentró *en vacío* a 40°C para dar el material crudo (1,27g, 3,61mmol). El producto crudo se purificó mediante tratamiento con carbón vegetal (1 g) en DCM (120mL) y cromatografía de columna (sílice; gradiente de elución, 100% EtOAc a 50% en DCM a EtOAc:DCM:MeOH; 2:10:1) para dar el producto deseado como un sólido blancuzco (305mg, 0,87mmol, 15%) (pureza 99%)

^{1}H NMR (360MHz, d^6-DMSO) δ 1,40-1,53 (m, 1H), 1,65-1,78 (m, 2H), 1,85-2,0 (m, 5H), 2,2 (m, *J* = 7,3, 6,3Hz, 2H), 2,45 (s, 6H), 2,67 (t, *J* = 7,3Hz, 2H), 2,75 (ddd, *J* = 4,6, 13,6 & 13,6Hz, 2H), 4,22 (t, *J* = 6,3Hz, 2H), 5,71-5,75 (br s, 1H),

6,68 (d, J = 9,1Hz, 1H), 7,16-7,20 (br s, 1H), 7,35 (d, J = 9,1Hz, 1H).

Ejemplo 73

8'-Cloro-5'-etoxicarbonilmetoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CO_2CH_2CH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (0,5 g, 1,96 mmol) en DMF (10 mL) de 18 a 20°C se agregó carbonato de potasio (0,6 g, 4,31 mmol) y bromoacetato de etilo (0,36 g, 2,16 mmol). La mezcla se calentó a 100°C durante 1,5 horas, se enfrió a temperatura ambiente y luego se agregó agua (100 mL). El sólido resultante se filtró y se lavó con agua (50 mL) y heptano (20 mL). El secado en vacío a 50°C dio el compuesto del título (0,6 g, 1,7 mmol, 87%) como un sólido blancuzco.

^{1}H NMR (360 MHz, $CDCl_3$) δ 7,2 (d, J = 9,1 Hz, 1H), 7,03 (s, 1H), 6,37 (d, J = 9,1 Hz, 1H), 5,60 (s, 1H), 4,64 (s, 2H), 4,30 (q, J = 7,3 Hz, 2H), 2,70 (td, J = 13,2, 4,1 Hz, 2H), 1,80 (m, 4H), 1,55 (m, 3H), 1,45 (m, 1H), 1,35 (t, J = 7,3 Hz, 3H).

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Ejemplo 74

5'-Carboximetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2CO_2H, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solución de hidróxido de potasio (0,32 g, 5,65 mmol) en agua (1,1 mL) se agregó a una suspensión agitada del Ejemplo 73 crudo (0,4 g, 1,13 mmol) en THF (30 mL) a temperatura ambiente. La mezcla se agitó durante 24 horas antes de remover la THF mediante evaporaciín en vacío a 40°C. Se agregó agua (20 mL) al residuo y la mezcla se lavó una vez con acetato de etilo (10 mL). La solución acuosa se acidificó a pH 1 con ácido clorhídrico concentrado para dar un sólido blancuzco. El sólido se filtró y se lavó con agua (10 mL) y heptano (5 mL). El sólido se purificó mediante cromatografía de columna (sílice 10 g, eluyendo con 10% ácido acético en acetato de etilo) para dar el compuesto del título (0,15 g, 0,46 mmol, 41%) como un sólido blancuzco después de secar en vacío a 50°C. (pureza 98,9%) Punto de fusión = 284°C-286°C.

^{1}H NMR [$(CD_3)_2SO$] δ 13,05 (br s, 1H), 7,95 (br s, 1H), 7,24 (d, *J* = 9,0 Hz, 1H), 6,99 (br s, 1H, NH), 6,54 (d, *J* = 9,0 Hz, 1H), 4,69 (s, 2H), 2,61 (m, 2H), 1,77 (m, 2H), 1,55 (m, 3H), 1,45 (m, 2H), 1,30 (m, 1H).

Ejemplo 75

5'-Carboxipropoxe-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2CH_2CO_2H$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 63 (1,07 g, 4 mmol) en DMF (20 mL) de 18°C a 20°C se agregó carbonato de potasio (1,22 g, 8,8 mmol) y 4-bromobutirato de etilo (0,82 g, 4,2 mmol). La mezcla se calentó a 100°C durante 2 horas, se enfrió a temperatura ambiente y se agregó a agua (200 mL). La mezcla se extrajo con acetato de etilo (2 x 200 mL). Los extractos orgánicos combinados se lavaron con agua (100 mL), se escaron sobre sulfato de magnesio y se evaporaron *en vacío* a 50°C para dar un residuo sólido. La trituración del residuo con heptano (10 mL) dio el intermedio etil éster (1,27 g, 3,33 mmol, 84%) como un sólido rosa después de secar *en vacío* a 50°C.

^{1}H NMR (360 MHz, $CDCl_3$) δ 1,11 (t + m, 4H), 1,38 (m, 2H), 1,58 (m, 5H), 2,01 (m, 2H), 2,38 (m, 4H), 3,87 (t, *J* = 5,7Hz, 2H), 4,01 (q, *J* = 6,3Hz, 2H), 5,46 (s, 1H), 6,32 (d, *J* = 8,1Hz, 1H), 6,87 (s, 1H), 7,02 (d, *J* = 8,1Hz, 1H).

6N-Ácido clorhídrico (10 mL) se agregó a una suspensión agitada del etil éster (0,9 g, 2,36 mmol) en dioxano (6 mL) de

18°C a 20°C. La mezcla se agitó bajo reflujo durante 2,5 horas. Después de enfriar de 18°C a 20°C el sólido se filtró y se lavó con agua (50 mL) y TBME (5 mL). El sólido se trituró con TBME (30 mL) para dar el compuesto del título (0,64 g, 1,79 mmol, 76%) como un sólido blancuzco después de secar *en vacío* a 50°C. (pureza 98%).

^{1}H NMR (360 MHz, d_6 DMSO) δ 1,03 (m, 1H), 1,34 (m, 2H), 1,47 (m, 3H), 1,68 (m, 2H), 1,80 (m, 2H), 2,30 (m, 4H), 3,87 (t, *J* = 6,3Hz, 2H), 6,40 (d, *J* = 9,0 Hz, 1H), 6,90 (s, 1H), 7,11 (d, *J* = 9,0 Hz, 1H), 7,80 (s, 1H), 12,05 (br s, 1H).

Ejemplo 76

8'-Cloro-5'-(3-sulfopropoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2CH_2SO_3H$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto el título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (1 g, 3,93 mmol) en DMF (20 mL) de 18°C a 20°C se agregó carbonato de potasio (1,19 g, 8,65 mmol) y luego 3-bromopropanosulfonato de sodio (0,97 g, 4,32 mmol). La mezcla se calentó a 100°C durante 6 horas, se enfrió a temperatura ambiente y luego se agregó a agua (300 mL). La solución resultante se acidificó a pH 1 con ácido

clorhídrico concentrado. La mezcla acuosa se lavó con acetato de etilo (200 mL) y se evaporó en vacío hasta secarse a 70°C. El residuo se trató con TBME (200 mL) y una pequeña cantidad de sólido blanco se filtró y se descartó. La decantación del TBME del filtrado aisló un aceite insoluble amarillo pálido. La DMF restante se removió del aceite mediante una nueva evaporación en vacío a 70°C. La goma resultante se trituró con acetonitrilo (10 mL) para dar el compuesto del título (0,11 g, 0,28 mmol, 7%) como un sólido blanco después de secar en vacío a 50°C.

(pureza = 99,7%)

^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 8.27 (br s, 1H), 7,95 (s, 1H), 7,25 (d, *J* = 8,6 Hz, 1H), 7,04 (s, 1H), 6,63 (d, *J* = 8,6 Hz, 1H), 4,09 (t, *J* = 6,5 Hz, 2H), 2,64 (t, *J* = 7,5 Hz , 2H), 2,58 (m, 2H), 2,08 (m, 2H), 1,80 (br m, 2H), 1,60 (br m, 3H), 1,38 (br d, *J* = 12,6 Hz, 2H), 1,22 (m, 1H).

Ejemplo 77

8'-Cloro-5'-[2-(tetrahidro-piran-2-iloxi)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2CH_2O-(tetrahidro-piran-2-ilo), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (0,5 g, 1,96 mmol) en DMF (10 mL) de 18 a 20°C se agregó carbonato de potasio (0,6 g, 4,31 mmol) luego 2-(2-bromoetoxi)tetrahidro-2H-pirano (0,45 g, 2,16 mmol). La mezcla se calentó a 100°C durante 3,2 hours, se enfrió a temperatura ambiente y luego se agregó a agua (100 mL). El sólido resultante se filtró y se lavó con agua (50 mL) y luego con heptano (20 mL). El secado en vacío a 50°C dio el compuesto del título (0,69 g, 1,75 mmol, 90%) como un sólido blancuzco.

^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 7,94 (s, 1H), 7,21 (d, *J* = 8,9 Hz, 1H), 6,99 (s, 1H), 6,59 (d, *J* = 8,9 Hz, 1H), 4,68 (m, 1H), 4,08 (m, 2H), 3,92 (m, 1H), 3,70 (m, 2H), 3,41 (m, 1H), 2,56 (td, *J* = 13,6, 4,1 Hz, 2H), 1,33 - 1,84 (m, 13H), 1,19 (m, 1H).

Ejemplo 78

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Formula (I): X_1=C-OCH_2CH_2OH, X_2=CH, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

El ejemplo 77 (0,69 g, 1,75 mmol) se agitó en una mezcla de THF (20 mL) y agua (4 mL). Se agregó ácido clorhídrico

concentrado (0,4 mL) y la mezcla se agitó a temperatura ambiente durante 24 h luego se calentó a reflujo durante 2 horas. La THF se removió mediante evaporaciín en vacío a 40°C y el residuo se particionó entre agua (25 mL) y acetato de etilo (40 mL). La fase acuosa se separó y se extrajo con acetato de etilo (20 mL). Los extractos combinados se lavaron con agua (20 mL), se secaron sobre $MgSO_4$ y la concentración en vacío a 40°C dio el compuesto del título (0,32 g, 1,03 mmol, 59%) como un sólido color crema después de secar en vacío a 50°C.

(pureza = 95,7%) Punto de fusión = 176°C-178°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,89 (br s, 1H), 7,23 (d, *J* = 9,0 Hz, 1H), 6,98 (br s, 1H, NH), 6,63 (d, *J* = 9,0 Hz, 1H), 4,81 (t, *J* = 5 Hz, 2H), 4,00 (t, *J* = 5 Hz, 2H), 3,76 (q, *J* = 5 Hz, 2H), 2,58 (m, 2H), 1,77 (m, 2H), 1,53 (m, 3H), 1,45 (m, 2H), 1,30 (m, 1H).

Ejemplo 79

8'-Cloro-5'-(5-etoxicarbonil-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2-(5-etoxicarbonil-furan-2-ilo), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (0,5 g, 1,87 mmol) y

yoduro de sodio (0,14 g, 1,87 mmol) en DMF (10 mL) de 18°C a 20°C se agregó carbonato de potasio (0,258 g, 0,95 mmol) y 5-etil éster del ácido clorometil-furan-2-carboxílico (0,29 mL, 1,87 mmol). La mezcla se agitó a temperatura ambiente durante 2 h. Después de completar, el solvente se removió bajo presión reducida y se agregó una mezcla de agua y EtOAc. La capa se separó, la acuosa se extrajo tres veces con EtOAc. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El sólido se purificó mediante cromatografía de columna (sílice 10 g, eluyendo con CH_2Cl_2/MeOH: 99/1 a 98/2) para dar el compuesto del título (0,75 g, 96%) como un sólido blanco después de secar en vacío a 50°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,98 (br s, 1H, NH), 7,30-7,28 (m, 2H), 7,01 (br s, 1H, NH), 6,80-6,76 (m, 2H), 5,2 (s, 2H), 4,28 (q, *J* = 7,0 Hz, 2H), 2,43-2,4 (m, 2H), 1,75-1,72 (m, 2H), 1,56-1,53 (m, 3H), 1,40 (m, 2H), 1,28 (t, *J* = 7,0 Hz, 3H), 0,97 (m, 1H).

Ejemplo 80

8'-Chloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2-(5-carboxi-furan-2-ilo), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Una solución de hidróxido de litio monohidratado (0,85 g, 20 mmol) en agua (1,35 mL), EtOH (11 mL) y MeOH (67 mL) se agregó a una suspensión agitada del Ejemplo 79 crudo (0,6 g, 1,43 mmol) en CH_2Cl_2 (17 mL) a temperatura ambiente. La mezcla se agitó durante 48 h antes de que los solventes se removieran mediante evaporación en vacío a 40°C. Se agregó agua al residuo y la mezcla se acidificó con HCl acuoso concentrado y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El sólido se purificó mediante cromatografía de columna (sílice 5 g, eluyendo con CH_2Cl_2/MeOH: 70/30) para dar el compuesto del título (0,05 g, 9%) como un sólido blanco después de secar en vacío a 50°C. (pureza 98%)

^{1}H NMR [$(CD_3)_2SO$] δ 13,10 (s, 1H), 7,96 (br s, 1H, NH), 7,29 (d, *J* = 9,1 Hz, 1H), 7,12 (br s, 1H, NH), 6,99 (s, 1H), 6,79 (d, *J* = 9,1 Hz, 1H), 6,70 (br s , 1H), 5,15 (s, 2H), 2,43-2,40 (m, 2H), 1,70 (m, 2H), 1,55-1,52 (m, 3H), 1,40 (m, 2H), 0,98-1,00 (m, 1H).

Ejemplo 81

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2CN, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

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El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 63 (2 g, 7,85 mmol) en DMF (30 mL) de 18°C a 20°C se agregó carbonato de potasio (2,39 g, 17,3 mmol) y luego bromoacetonitrilo (1,04 g, 8,64 mmol). La mezcla se calentó a 100°C durante 2 horas, se enfrió de 18°C a 20°C y se agregó a agua (300 mL). El sólido resultante se filtró y se lavó con agua (60 mL). El secado al vacío a 50°C dio el el compuesto del título crudo (2,35 g). El producto crudo se purificó mediante cromatografía de columna (sílice 70 g eluyendo con 10% metanol en diclorometano) para dar el compuesto del título (1,72 g, 5,6 mmol, 72%) como un sólido color cervato después de secar en vacío a 50°C.

(pureza = 97%) Punto de fusión = 193°C-195°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,12 (br s, 1H), 7,36 (d, *J* = 9,0 Hz, 1H), 7,07 (br s, 1H, NH), 6,75 (d, *J* = 9,0 Hz, 1H), 5,24 (s, 2H), 2,34 (m, 2H), 1,80 (m, 2H), 1,63 (m, 3H), 1,47 (m, 2H), 1,20 (m, 1H).

Ejemplo 82

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2-(1H-tetrazol-5-yl), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El Ejemplo 81 (0,05 g, 0,16 mmol), trimetiltin azida (0,05 mL, 0,179 mmol) y tolueno (2 mL) se mezclaron y refluyeron bajo nitrógeno durante 15 h. Se agregó 10M NaOH (0,02 mL, 0,2 mmol) y la mezcla se agitó a temperatura ambiente toda la noche. La capa superior se removió, se agregó hexano al residuo, la mezcla resultante se agitó durante 30 minutos, se removió el hexano. Esta operación se repitió tres veces, y se agregó EtOAc, el precipitado se filtró y se lavó con EtOAc. El residuo se tomó en CH_2Cl_2 y 1M HCl (1 mL, 1 mmol) y se concentró bajo presión reducida. El precipitado se lavó sucesivamente con agua y MeOH para dar el compuesto del título (0,04 g, 71%) como un polvo blanco (pureza = 98,1%) Punto de fusión = 287°C-289°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,02 (br s, 1H), 7,34 (d, *J* = 8,9 Hz, 1H), 7,01 (br s, 1H), 6,82 (d, *J* = 8,9 Hz, 1H), 5,47 (s, 2H), 2,35 (m, 2H), 1,73 (m, 2H), 1,50 (m, 3H), 1,36 (m, 2H), 0,88 (m, 1H).

Ejemplo 83

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_2-(5-hidroxi-[1,2,4]oxadiazol-3-ilo), X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

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Preparación de 8'-cloro-5'-(N-hidroxicarbamimidoilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (intermedio 9)

A una mezcla del Ejemplo 81 (0,6 g, 1,96 mmol) y clorhidrato de hidroxilamina (0,186 g, 2,94 mmol) en etanol (7 mL) se agregó hidróxido de sodio (0,114 g, 2,85 mmol) disuelto en el mínimo de agua. La mezcla de la reacción se calentó a reflujo durante 24 h con agitación. Después de enfriar, el solvente se concentró bajo presión reducida. El residuo se recogió en CH_2Cl_2, el precipitado se filtró, se lavó con CH_2Cl_2 y se secó bajo vacío a 45°C para lograr el intermedio 9 en un rendimiento cuantitativo.

^{1}H NMR [$(CD_3)_2SO$] δ 9,34 (br s, 1H, OH), 7,94 (br s, 1H, NH), 7,73 (d, *J* = 9,0 Hz, 1H), 6,98 (br s, 1H, NH), 6,70 (d, *J* = 9,0 Hz, 1H), 5,61 (s, 2H), 4,40 (br s, 2H, NH_2), 2,58-2,54 (m, 2H), 1,83-1,72 (m, 2H), 1,62-1,53 (m, 3H), 1,46 (m, 2H), 1,24-1,07 (m, 1H).

Preparación del Ejemplo 83

A una mezcla del intermedio 9 (0,3 g, 0,885 mmol) cloroformato de etilo (0,13 mL, 1,3 mmol) en $CHCl_3$ anhidro (4 mL) se agregó trietilamina (0,22 mL, 1,6 mmol). La mezcla de la reacción se agitó a temperatura ambiente durante 5 h. Después de completar, el precipitado se filtró para lograr el intermedio

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(etoxicarbonil)oxi]amino (0,275 mg, 76%), que se usó directamente en el paso siguiente sin nueva purificación.

^{1}H NMR [$(CD_3)_2SO$] δ 7,98 (br s, 1H, NH), 7,30 (d, *J* = 9,0 Hz, 1H), 6,98 (br s, 1H, NH), 6,78 (br s, 2H, NH_2), 6,70 (d, *J* = 9,0 Hz, 1H), 4,48 (s, 2H), 4,20 (q, *J* = 7,7 Hz, 2H), 2,58-2,54 (m, 2H), 1,83-1,72 (m, 2H), 1,62-1,53 (m, 3H), 1,46 (m, 2H), 1,28-1,20 (m, 1H), 1,23(t, *J* = 7,7 Hz, 3H).

Una mezcla del intermedio [(etoxicarbonil)oxi]amino (0,275 g, 0,67 mmol) y 1,8-diazabiciclo[5,4,0] undec-7-eno (0,4 mL, 2,67 mmol) en CH_3CN (4 mL) se refluyó durante 24h con agitación. La mezcla de la reacción se concentró bajo presión reducida y se recogió en una mezcla de CH_2Cl_2 1M HCl acuoso. Las capas se separaron y la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron para dar el compuesto del título (0,17 g, 70%) como un sólido blanco después de secar en vacío a 50°C.

^{1}H NMR [$(CD_3)_2SO$] δ 12,86 (br s, 1H), 8,04 (br s, 1H), 7,32 (d, *J* = 9,0 Hz, 1H), 7,03 (br s, 1H), 6,72 (d, *J* = 9,0 Hz, 1H), 5,07 (s, 2H), 2,42-2,36 (m, 2H), 1,78-1,74 (m, 2H), 1,59-1,56 (m, 3H), 1,44 (m, 2H), 1,11 (m, 1H).

Ejemplo 84

8'-Cloro-6'-yodo-5'-[2-dimetilamino-etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-$OCH_2CH_2N(CH_3)_2$, X_2=C-I, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo L. A una solución agitada del Ejemplo 68 (1,5 g, 4,44 mmol) en ácido trifluoroacético (15 mL) se agregaron sucesivamente N-yodosuccinimida (1,1 g, 4,89 mmol, 1,1 equiv.) y ácido sulfúrico (4 mL). La solución resultante se agitó durante 4 h, y luego se agregaron acetato de etilo y agua. La capa orgánica se separó. La capa acuosa se lavó dos veces con etilo, se basificó a pH 9 con hidróxido de sodio acuoso al 30% y luego se extrajo tres veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con agua, solución salina y se concentraron bajo presión reducida para dar 1,95 g (95%) del compuesto del título como un sólido blanco (pureza 99%)

^{1}H NMR (CDCl3) δ 7,71 (s, 1H), 7,06 (br s, 1H), 5,43 (br s, 1H), 4,06 (t, *J* = 6,0 Hz, 2H), 2,82 (t, *J* = 6,0 Hz, 2H), 2,36 (s, 6H), 2,34 (m, 2H), 1,93 (m, 2H), 1,80-1,71 (m, 3H), 1,59-1,50 (m, 2H), 1,33 (m, 1H).

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Ejemplo 85

6'-(4-Carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=C-(4-carboxifenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo G. A una solución agitada del Ejemplo 65 (7 g, 17,2 mmol) en DMF (84 mL) de 18°C a 20°C se agregó una solución de ácido 4-carboxifenil-borónico (343 mg, 20,64 mmol) y carbonato de potasio (2M, 34 mL, 68 mmol) bajo N_2. Después de desgasificar la mezcla hirviendo con N_2 durante 2 h, se agregó tetrakis (trifenilfosfino) paladio (1,33 g, 1,147 mmol). La solución se calentó a 100°C durante 18 h. Luego se le agregó agua (1L) y EtOAc (1L). El producto deseado se precipitó y se recogió mediante filtración para dar el producto crudo (3,5 g, 51%). El filtrado acuoso se separó y se acidificó a pH 1 con HCl concentrado (20 mL). El sólido blanco se recogió mediante filtración (2,7 g, 39%). Los productos crudos se combinaron y se purificaron mediante cromatografía de columna (sílice 80 g; gradiente de elución, 20% DCM en EtOAc a 50% DCM en MeOH) para dar el compuesto del título (1,77 g, 4,41 mmol, 18%) como un sólido blancuzco. (pureza = 99,4%) Punto de fusión = 309°C-311°C.

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^{1}H NMR [$(CD_3)_2SO$] δ 8,27 (s, 1H), 7,98 (d, *J* = 8,0 Hz, 2H), 7,50 (d, *J* = 8,0 Hz, 2H), 7,29 (s, 1H), 6,98 (s, 1H), 3,18 (s, 3H), 2,25 (m, 2H), 1,80 (m, 4H), 1,61 (m, 1H), 1,48 (m, 2H), 1,19 (m, 1H).

Ejemplo 86

6'-(3-Carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=C-(3-carboxifenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo G. A una solución agitada del Ejemplo 65 (1,75 g, 4,30 mmol) en DMF (30 mL) de 18°C a 20°C se agregó a una solución de ácido 3-carboxifenil-borónico (0,86 g, 5,18 mmol) y carbonato de potasio (2M, 8,5 mL, 17mmol) bajo N_2. La mezcla se desgasificó hirviendo N_2 durante 2 h y se agregó tetrakis(trifenilfosfino)paladio (331 mg, 0,286 mmol). La solución se calentó a 100°C durante 24 h y se dejó enfriar de 18°C a 20°C. La mezcla de la reacción se agregó a agua (200 mL) y EtOAc (300 mL). El producto deseado se precipitó y se recogió mediante filtración, se secó en vacío a 40°C para dar el compuesto del título (567 mg, 1,42 mmol, 33%) como un sólido marrón claro.

(pureza = 96%)

^{1}H NMR ($(CD_3)_2SO$) δ 13,06 (br s, 1H), 8,30 (br s, 1H), 8,04 (s, 1H), 7,94 (d, *J* = 8,1 Hz, 1H), 7,74 (d, *J* = 8,0 Hz, 1H), 7,58 (t, *J* = 8,0 Hz, 1H), 7,34 (s, 1H), 7,01 (br s, 1H), 3,21 (s, 3H), 2,30 (m, 2H), 1,87-1,78 (m, 4H), 1,67-1,64 (m, 1H), 1,53-1,50 (m, 2H), 1,24 (m, 1H).

Ejemplo 87

8'-Cloro-6'-[2-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-(2-(4-metil-piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de (2-bromo-fenil)-(4-metil-piperazin-1-il)-metanona (intermedio 10)

A una solución de cloruro de 2-bromobenzoilo (2 g, 9 mmol) en tolueno (30 mL) se agregó N-metilpiperazina (2 mL, 18 mmol, 2 equiv.). La mezcla resultante se agitó toda la noche. El precipitado se filtró y el filtrado se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó con agua. La capa orgánica se concentró bajo presión reducida para dar 2g (77% de rendimiento) del intermedio 10.

^{1}H NMR [CDCl3] δ 7,60 (m, 1H), 7,35 (m, 1H), 7,20 (m, 2H), 3,90-3,80 (m, 2H), 3,40-3,20 (m, 2H), 2,60-2,40 (m, 3H), 2,30 (s, 3H), 2,30-2,25 (m, 1H).

Preparación del Ejemplo 87

A una suspensión del Ejemplo 25 (200 mg, 0,5 mmol) en dimetilformamida (6 mL) se agregaron sucesivamente acetato de sodio (130 mg, 1,6 mmol, 3 equiv.) y bis(pinacolato)diboro (152 mg, 0,6 mmol). La mezcla se desgasificó hirviendo nitrógeno y se agregó tetrakis(trifenilfosfino)paladio (30 mg, 0,026 mmol, 0,05 equiv.). La mezcla resultante se calentó a 45°C toda la noche y a 90°C durante 2 h, se concentró bajo presión reducida. El residuo se recogió en diclorometano, se lavó una vez con agua. La capa orgánica se secó sobre sulfato de sodio, se concentró bajo presión reducida y se purificó mediante cromatografía rápida sobre gel de sílice (heptano/ acetato de etilo : 80/20), el sólido resultante se hidrolizó con ácido clorhídrico (1N) en metanol y se concentró bajo presión reducida para dar 400 mg (66% de rendimiento) del ácido borónico. A una suspensión del ácido borónico crudo (40 mg, 0,14 mmol) en dimetilformamida (2 mL) se agregaron sucesivamente el intermedio 10 (46 mg, 0,16 mmol, 1,2 equiv.) y una solución acuosa 2M de carbonato de potasio (0,2 mL, 0,4 mmol, 3 equiv.). La mezcla se desgasificó hirviendo nitrógeno y se agregó tetrakis(trifenilfosfino)paladio (8 mg, 0,007

mmol, 0,05 equiv.). Después de calentar a 90°C durante 3 horas, la mezcla se concentró bajo presión reducida, se recogió en acetato de etilo y se lavó con agua. La capa orgánica se lavó dos veces con HCl (1N). La capa acuosa se basificó a pH 9 y se extrajo tres veces con diclometano. La capa orgánica se concentró bajo presión reducida, el sólido resultante se cristalizó en tolueno/metanol para dar 10 mg (16% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión =250°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,58 (br s, 1H, NH), 7,50-7,49 (m, 2H), 7,43 (m, 1H), 7,33-7,28 (m, 3H), 7,18(br s, 1H, NH), 3,70 (m, 1H), 3,20 (m, 1H), 2,95 (m, 1H), 2,78 (m, 1H), 2,38 (m, 1H), 2,10 (m, 1H), 1,98 (s, 3H), 1,86-1,75 (m, 6H), 1,62-1,48 (m, 4H), 1,24-1,16 (m, 2H).

Ejemplo 88

8'-Cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-(2-metil-4-(4-metil-piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de (4-Bromo-3-metil-fenil)-(4-metil-piperazin-1-il)-metanona (intermedio 11)

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A una solución de cloruro de 4-bromo-3-metilbenzoilo (0,5 g, 2 mmol) en tolueno (6mL) se agregó N-metilpiperazina (0,5 mL, 4 mmol, 2 equiv.). La mezcla resultante se agitó toda la noche. El precipitado se filtró y el filtrado se concentró bajo presión reducida. El residuo se recogió en acetato de etilo y se lavó con agua. La capa orgánica se secó sobre sulfato de sodio, se concentró bajo presión reducida para dar 0,2 g (34% de rendimiento) del intermedio 11.

Preparación del Ejemplo 88

A una suspensión del Ejemplo 25 (1 g, 2,5 mmol) en dimetilformamida (25 mL) se agregaron sucesivamente acetato de sodio (650 mg, 8 mmol, 3 equiv.) y bis(pinacolato)diboro (760 mg, 3 mmol, 1,2 equiv.). La mezcla se desgasificó hirviendo nitrógeno y se agregó tetrakis(trifenilfosfino) paladio (150 mg, 0,13 mmol, 0,05 equiv.). La mezcla resultante se calentó a 45°C toda la noche, luego se agregaron bis(pinacolato)diboro (635 mg, 2,5 mmol, 1 equiv.) y tetrakis(trifenilfosfino) paladio (100 mg, 0,087 mmol, 0,035 equiv.) adicionales. La mezcla se calentó a 90°C toda la noche y se concentró bajo presión reducida. El residuo se recogió en acetato de etilo, se lavó una vez con agua. La capa orgánica se concentró bajo presión reducida y el sólido resultante se lavó con acetato de etilo para dar 0,7 g (78% de rendimiento) de boronato. A una suspensión del boronato (200 mg, 0,5 mmol) en dimetilformamida

(3 mL) se agregaron sucesivamente intermedio 11 (200 mg, 0,7 mmol, 1,4 equiv.) y acetato de sodio (123 mg, 1,5 mmol, 3 equiv.). La mezcla se desgasificó hirviendo nitrógeno y se agregó tetrakis(trifenilfosfino)paladio (29 mg, 0,025 mmol, 0,05 equiv.). Después de calentar a 90°C toda la noche, la mezcla se concentró bajo presión reducida, se recogió con diclorometano y se lavó con agua. La capa orgánica se concentró bajo presión reducida y se purificó mediante cromatografía sobre gel de sílice (diclorometano/metanol : 97/3 a 95/5) y el sólido resultante se cristalizó en tolueno/metanol para dar 10 mg (6% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión = 184°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,50 (br s, 1H, NH), 7,30-7,23 (m, 5H), 7,15 (br s, 1H, NH), 3,60-3,37 (m, 4H), 2,33-2,27 (m, 7H), 2,20 (s, 3H), 1,78 (m, 6H), 1,62 (m, 1H), 1,5 (m, 2H), 1,24 (m, 1H).

Ejemplo 89

8'-Cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-(4-(piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (400 mg, 1,08 mmol) en tolueno (4 mL) se agregó cloruro de tionilo (0,2 mL, 2,16 mmol, 2

equiv.). La mezcla resultante se calentó a reflujo durante 3 h, luego se concentró bajo presión reducida y se recogió en THF (8 mL). A una solución de 0,135 M de cloruro de acilo en THF (4 mL, 0,54 mmol) se agregó trietilamina (0,1 mL, 0,15 mmol, 3 equiv.) y piperazina (70 mg, 0,81 mmol, 1,5 equiv.). Después de agitar durante 2 días, la mezcla se concentró, se recogió en diclorometano, se lavó con agua y se extrajo con una solución acuosa 1N de HCl. La capa acuosa se lavó dos veces con diclorometano, se basificó a pH 9 y se extrajo tres veces con diclorometano. Los extractos orgánicos combinados se concentraron bajo presión reducida y se purificaron mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/MeOH : 99/1 a 95/5) para dar 181 mg (75% de rendimiento) del compuesto del título como un sólido blanco.

^1H NMR [$(CD3)_2SO$] δ 8,54 (br s, 1H, NH), 7,78 (d, *J* = 8,5 Hz, 2H), 7,66 (s, 1H), 7,63 (s, 1H), 7,48 (d, *J* = 8,0 Hz, 2H), 7,17 (br s, 1H, NH), 3,57 (br m, 4H), 2,96 (br m, 4H), 1,88 - 1,77 (m, 6H), 1,64 (m, 1H), 1,54 (m, 2H), 1,28 (m, 1H).

Ejrmplo 90

8'-Cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-(4-carbamoil-fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (1g, 2,7 mmol) en tolueno (10 mL) se agregó cloruro de tionilo (0,4 mL, 5,4 mmol, 2equiv.). La mezcla resultante se calentó a reflujo toda la noche. El precipitado se aisló mediante filtración, se lavó con tolueno y se secó bajo presión reducida para dar 0,9 g (90% de rendimiento) de cloruro de acilo. A una suspensión del cloruro de acilo (100 mg, 0,25 mmol) en tolueno (2 mL) se agregó una solución 0,5M de amoníaco en dioxano (1 mL, 0,5 mmol, 2 equiv.). La mezcla se agitó toda la noche y se concentró bajo presión reducida. El residuo se recogió en diclorometano y se lavó con agua. La capa orgánica se concentró bajo presión reducida y el sólido resultante se purificó mediante cromatografía rápida sobre gel de sílice (diclorometano/metanol : 97/3) para dar 10 mg (66% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión =327°C

^{1}H NMR [$(CD_3)_2SO$] δ 8,55 (br s, 1H, NH), 8,02 (br s, 1H, NH), 7,95-7,93 (d, *J* = 8,5Hz, 2H), 7,80-7,77 (d, *J* = 8,5Hz, 2H), 7,69 (s, 1H), 7,63 (s, 1H), 7,36 (br s, 1H, NH), 7,17 (br s, 1H, NH), 1,92-1,77 (m, 6H), 1,66-1,63 (m, 1H), 1,55-1,53 (m, 2H), 1,32-1,23 (m, 1H),

Ejemplo 91

8'-Cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-(4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión del Ejemplo 32 (150 mg, 0,4 mmol) en tolueno (2 mL) se agregó cloruro de tionilo (0,06 mL, 0,8 mmol, 2 equiv.). La mezcla resultante se calentó a reflujo durante 3 horas, y luego se concentró bajo presión reducida. El sólido resultante se agregó a una solución de 1-(N-metil-piperidin-4-il) piperazina (100 mg, 0,6 mmol, 1,5 equiv.) y triethylamine (0,1 mL, 0,8 mmol, 2 equiv.) en tolueno (2 mL). Después de agitar toda la noche, la mezcla se diluyó con diclorometano y se lavó con una solución saturada de bicarbonato de sodio. La capa orgánica se concentró bajo presión reducida. El sólido resultante se lavó con acetato de etilo/metanol y se cristalizó en acetato de etilo/metanol para dar 70 mg (33% de rendimiento) del compuesto del título como un sólido blanco. Punto de fusión =181°C.

^{1}H NMR [$(CD_3)_2SO$] δ 8,53 (br s, 1H, NH), 7,75 (d, *J* = 8Hz, 2H), 7,65 (s, 1H), 7,60 (s, 1H), 7,43 (d, *J* = 8Hz, 2H), 7,17 (br s,

1H, NH), 3,59-3,31 (br m, 7H), 2,78-2,75 (m, 2H), 2,16-2,12 (m, 4H), 1,88-1,29 (m, 17H).

Ejemplo 92

8'-Cloro-5'-metoxi-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=C-OCH_3, X_2=C-(4-(4-metil-piperazin-1-carbonil)fenilo), X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 85 (1 g, 2,55 mmol) en DCM (15 mL) de 18°C a 20°C se agregó una solución de cloruro de tionilo (0,6 g, 5 mmol) y DMF (0,8 mL). La mezcla se agitó de 18°C a 20°C durante 2 h. La mezcla resultante se concentró *en vacío a* 55°C. Se agregó tolueno (10mL) al intermedio y se concentró *en vacío* a 55°C. (Este procedimiento se repitió para garantizar que todo el cloruro de tionilo sin reaccionar se removiera.). El intermedio crudo se disolvió en tolueno (10mL) y se agregó N-metil piperazina (0,5g, 5 mmol). La mezcla de la reacción se agitó durante 15 h de 18°C a 20°C y se concentró *en vacío* a 55°C. El producto crudo se purificó mediante cromatografía de columna (sílice 35g; 60% EtOAc en MeOH) para

dar el compuesto del título como un sólido marrón pálido (170mg, 0,35mmol, 14%) (pureza 95%).

^{1}H NMR [$(CD_3)_2SO$] δ 1,25 (m, 1H), 1,54 (m, 2H), 1,68 (m, 1H), 1,83 (m, 4H), 2,22 (s, 3H), 2,32 (m, 6H), 3,25 (s, 3H), 3,36-3,40 (br s, 2H), 3,56-3,70 (br s, 2H), 7,05-7,09 (br s, 1H), 7,36 (s, 1H), 7,47 (d, *J* = 8,3Hz, 2H), 7,58 (d, *J* = 8,3Hz, 2H), 8,36-8,40 (br s, 1H).

Ejemplo 93

8-Cloro-5-metoxiespiro[4H-benzo[d][1,3]oxazin-2-ilamino-4-4'-(tetrahidro-piran-4'-ilo)]

Fórmula (III), X_1=C-OCH_3, X_2=CH, X_3=CH, X_4=C-Cl, A= tetrahidro-piran-4-ilo, X=O, Z^1=NH_2, Y=N

Preparación de N-(2-cloro-5-metoxi-fenil)-2,2-dimetil-propionamida (intermedio 12)

A una solución de clorhidrato de 2-cloro-5-metoxianilina (8 g, 41,1 mmol) y trietilamina (12,6 mL, 90,42 mmol) en CH_2Cl_2 (200 mL) cloruro de pivaloilo de nitrógeno (5,57 mL, 45,22 mmol) se agregó gota a gota a 0°C. La mezcla de la reacción se agitó a temperatura ambiente toda la noche. La mezcla se vertió en una solución acuosa de $NaHCO_3$ y se extrajo con CH_2Cl_2. Los extractos orgánicos se lavaron con una solución saturada acuosa de NaCl, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante

cromatografía rápida sobre gel de sílice (ciclohexano/EtOAc : 98/2) para lograr el intermedio 12 como un aceite rosa (7,54 g, 76%).

^{1}H NMR [$CDCl_3$] δ 8,15 (d, *J* = 3,0 Hz, 1H), 8,0 (br s, 1H), 7,17 (d, *J* = 9,0 Hz, 1H), 6,57 (dd, *J* = 9,0, 3,0 Hz, 1H), 3,79 (s, 3H), 1,33 (s, 9H).

Preparación de N-[6-cloro-2-(4-hidroxi-tetrahidro-piran-4-il)-3-metoxi-fenil]-2,2-dimetil-propionamida (intermedio 13)

A una solución agitada del intermedio 12 (1 g, 4,13 mmol) en THF (25 mL) bajo nitrógeno a -20°C se agregó gota a gota *n*-butillitio (2,5M en hexano, 4,13 mL, 10,34 mmol). La mezcla de la reacción se agitó a -10°C durante 4 h y se agregó *n*-butilitio (2,5M en hexano, 4,13 mL, 10,34 mmol) gota a gota a -10°C. La mezcla se agitó nuevamente durante 7 h y se agregó tetrahidropiran-4-ona gota a gota a 0°C. La mezcla se agitó toda la noche a temperatura ambiente, se vertió en agua y se extrajo con EtOAc. Los extractos orgánicos se lavaron con una solución acuosa saturada de NaCl, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se purificó mediante precipitación en EtOAc para lograr el intermedio 13 como un polvo blanco (0,25 g, 18%).

^{1}H NMR [$CDCl_3$] δ 8,08 (br s, 1H, NH), 7,32 (d, *J* = 8,5 Hz, 1H), 6,82 (d, *J* = 8,5 Hz, 1H), 3,95 (t, *J* = 11,5 Hz, 2H), 3,84 (s,

3H), 3,79 (m, 2H), 3,35 (m, 1H, OH), 2,86 (m, 1H), 2,33 (m, 1H), 1,84 (m, 2H), 1,33 (s, 9H).

Preparación de 6-cloro-2-(3,6-dihidro-2H-piran-4-il)-3-metoxi-fenilamina (intermedio 14)

Una solución del intermedio 13 (0,365 g, 1,06 mmol) e hidróxido de potasio (0,24 g, 4,27 mmol) en glicol (0,5 mL) se agitó a 100°C toda la noche. La mezcla de la reacción se vertió en agua y se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron. El producto crudo se purificó mediante cromatografía rápida de columna (eluyente: ciclohexano/ EtOAc : 90/10) para dar el compuesto del título (0,187 g, 73%) como un sólido blanco.

^{1}H NMR [$CDCl_3$] δ 7,09 (d, J = 9,0 Hz, 1H), 6,24 (d, J = 9,0 Hz, 1H), 5,71 (m, 1H), 4,29 (m, 2H), 4,20 (m, 2H), 3,92 (m, 2H), 3,73 (s, 3H), 2,29 (m, 2H).

Preparación de [6-cloro-2-(3,6-dihidro-2H-piran-4-il)-3-metoxi-fenil]-urea (intermedio 15)

Una solución del intermedio 14 (0,187 g, 0,78 mmol) y cianato de potasio (0,15 g, 1,95 mmol) en una mezcla de ácido acético (5 mL) y agua (0,5 mL) se agitó a temperatura ambiente toda la noche. El solvente se evaporó, y el residuo se recogió en una mezcla de CH_2Cl_2 y una solución saturada acuosa de $NaHCO_3$. Las

capas se separaron, la capa acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con solución salina, se secaron sobre Na_2SO_4 y se concentraron para dar 0,15 g (68%) del intermedio 15 crudo.

^1H NMR [$(CD_3)_2SO$] δ 7,51 (br s, 1H), 7,32 (d, J = 8,5 Hz, 1H), 6,89 (d, J = 8,5 Hz, 1H), 5,75 (br s, 2H), 5,49 (m, 1H), 4,12 (m, 2H), 3,74 (m, 5H), 2,16 (m, 2H).

Preparación de 8-cloro-5-metoxiespiro[4H-benzo[d][1,3]oxazin-2-ilamino-4-4'-(3'-yodo-tetrahidro-piran-4'-ilo)] (intermedio 16)

Una solución de yodo (0,23 g, 0,9 mmol) y yoduro de sodio (0,2 g, 1,35 mmol) en una solución acuosa de $NaHCO_3$ (10%) (3 mL) se agregó gota a gota a una solución agitada del intermedio 15 crudo (0,128 g, 0,45 mmol) en CH_2Cl_2 (5 mL) a temperatura ambiente. Después de otras 3 h, la mezcla de la reacción fue tratada con una pequeña cantidad de $Na_2S_2O_3$. Las capas se separaron y la acuosa se extrajo tres veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El material crudo se precipitó en Et_2O para dar intermedio 16 (0,1 g, 56%) como un sólido blanco después de secar en vacío a 50°C.

^1H NMR [$(CD_3)_2SO$] δ 7,26 (d, J = 8,8 Hz, 1H), 7,17 (br s, 2H), 6,59 (d, J = 8,8 Hz, 1H), 4,47 (m, 1H), 4,25 (dd, J = 10,3,

2,0 Hz, 1H), 3,97 (m, 1H), 3,82-3,79 (m, 2H), 3,75 (s, 3H), 3,70-3,62 (m, 1H), 1,81 (d, J = 14,6 Hz, 1H).

Preparación del Ejemplo 93

A una mezcla del intermedio 16 (100 mg, 0,24 mmol) y AIBN (0,02 g, 0,12 mmol) en tolueno (4 mL) bajo argón se agregó hidruro de tributiltina (0,08 mL, 0,29 mmol). La mezcla de la reacción se calentó a 80°C durante 10 h. Después de completar, la mezcla se concentró bajo presión reducida, el residuo se recogió en CH_3CN y se lavó tres veces con hexano. El producto crudo se purificó mediante cromatografía de columna rápida (eluyente: CH_2Cl_2/MeOH : 95/5) para dar el compuesto del título (31 mg, 46%) como un sólido blanco.

^{1}H NMR [$CDCl_3$] δ 7,22 (d, J = 9,0 Hz, 1H), 6,48 (d, J = 9,0 Hz, 1H), 5,29 (br s, 2H), 3,88-3,85 (m, 4H), 3,80 (s, 3H), 2,81-2,73 (m, 2H), 1,81 (d, J = 14 Hz, 2H).

Ejemplo 94

8'-Trifluorometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=CH; X_3=CH, X_4=C-CF_3, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo A usando 2-trifluorometilfenilurea (500 mg, 2,45 mmol), ácido

polifosfórico (3 g) y ciclohexanona (0,3 mL, 2,89 mmol). El producto crudo se purificó mediante cromatografía rápida sobre gel de sílice (hexano/EtOAc : 100/0 a 50/50) seguida por cromatografía de fase inversa sobre una columna de C_{18} (agua/acetonitrilo : 90/10 a 0/100) para dar el compuesto del título (13 mg, 2% de rendimiento).

^{1}H NMR [$CDCl_3$] δ 7,46 (m, 2H), 7,07 (m, 1H), 7,01 (br s, 1H, NH), 5,60 (br s, 1H, NH), 2,00 (m, 2H), 1,83-1,57 (m, 7H), 1,30 (m, 1H).

Ejemplo 95

8'-Cloro-6'-cianometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

Fórmula (I): X_1=CH, X_2=C-CH_2CN, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

El compuesto del título se preparó de acuerdo con el protocolo E. A una solución agitada del Ejemplo 7 (1 g, 4 mmol) en ácido acético glacial (15 mL) se agregó secuencialmente trioxano (0,55 g, 6 mmol, 1,5 equiv.) y una solución acuosa al 48% de ácido bromhídrico (5 mL). La mezcla se calentó a 95°C toda la noche, se vertió en hielo. El precipitado se filtró, se lavó dos veces con agua luego con éter para dar 1,39 g de 8'-Cloro-6'-bromometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona como un sólido blanco. El

derivado de bromometilo crudo (256 mg, 74 mmol) fue tratado con cianuro de sodio (40 mg, 82 mmol, 1,1 equiv.) en DMF (10 mL) y se calentó a 60°C durante dos horas. La mezcla se concentró bajo presión reducida, se recogió en agua, se extrajo dos veces con CH_2Cl_2, se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El material crudo se purificó dos veces mediante cromatografía rápida sobre gel de sílice (CH_2Cl_2/ MeOH: 99/1 seguido por ciclohexano/EtOAc : 60/40 + 2% NH_4OH), para dar el compuesto del título (60 mg, 28%) (pureza 95%) como un sólido blanco. Punto de fusión = 239°C

^1H NMR [$(CD_3)_2SO$] δ 8,50 (br s, 1H, NH), 7,30-7,29 (d, 2H), 7,15 (br s, 1H, NH), 3,94 (s, 2H), 1,81-1,68 (m, 7H), 1,54-1,50 (m, 2H), 1,25 (m, 1H).

Ejemplo 96

8'-Cloro-5'-(3-dimetilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-$OCH_2CH(OH)CH_2N(CH_3)_2$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

Preparación de 8'-Cloro-5'-(oxiran-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona (intermedio 17)

A una solución agitada del Ejemplo 63 (5g, 18,75mmol) en DMF (80mL) de 18°C a 20°C se agregó carbonato de potasio anhidro (6,5g, 46,9mmol) y luego epibromohidrina (2,83g, 20,6mmol) en una porción. La mezcla se calentó a 80°C durante 2 h y luego a 90°C durante 2h. El material crudo se enfrió en agua (800ml) y se extrajo con EtOAc (2x1L). La capa orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró *en vacío* a 40°C para dar el producto crudo (3,4g, 57% de rendimiento). El producto crudo se fue sometido a cromatografía de columna (sílice 100g, eluyendo con 30% a 50% EtOAc en heptano) para lograr el intermedio 17 (2,7g, 45% de rendimiento) como un sólido blanco después de secar *en vacío* a 45°C (pureza 98,9%).

^{1}H NMR [$CDCl_3$] δ 6,96 (d, *J* = 8,8 Hz, 1H), 6,76-6,79 (br s, 1H), 6,24 (d, *J* = 8,8 Hz, 1H), 5,30-5,35 (br s, 1H), 4,09 (dd, *J* = 2,8, 10,9 Hz, 1H), 3,67 (dd, *J* = 6,3, 10,9 Hz, 1H), 3,16 (m, 1H), 2,73 (dd, *J* = 4,3, 4,8 Hz, 1H), 2,53 (dd, *J* = 2,5, 4,8 Hz, 1H), 2,28-2,38 (m, 2H), 1,45-1,61 (m, 5H), 1,23-1,36 (m, 2H), 1,04-1,15 (m, 1H).

Preparación del ejemplo 96

A una solución agitada de dimetilamina en EtOH (17mL, 5,6M, 95,2mmol) de 18°C a 20°C se agregó el intermedio 17 (730mg, 2,26mmol) en una porción. La mezcla se calentó a 40°C durante 2,6 h. El sólido se filtró, se lavó con EtOH (40mL) y se secó

en vacío a 40°C para dar el producto deseado como un sólido blanco (515mg, 1,40mmol, 62%) (pureza 99%).

^{1}H NMR [$(CD_3)_2SO$] δ 7,10 (d, *J* = 9,0 Hz, 1H), 6,90-6,94 (br s, 1H), 6,42 (d, *J* = 9,0 Hz, 1H), 5,44-5,50 (br s, 1H), 3,99 (m, 1H), 3,91 (m, 2H), 3,50-3,54 (br s, 1H), 2,52 (m, 3H), 2,33 (dd, *J* = 12,1, 3,5 Hz, 1H), 2,27, (s, 6H), 1,59-1,76 (m, 5H), 1,38-1,52 (m, 2H), 1,18-1,30 (m, 1H).

Ejemplo 97

8'-Cloro-5'-(3-metilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-$OCH_2CH(OH)CH_2NHCH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada de metilamina en EtOH (12mL, 8M, 96mmol) de 18 a 20°C se agregó el intermedio 17 (500mg, 1,55mmol) en una porción. La mezcla se calentó a 40°C durante 2 h. Se agregó otra porción de metilamina en EtOH (10mL, 8M, 80mmol) y la reacción se calentó a 40°C durante otros 20 minutos. La mezcla se concentró *en vacío* a 40°C y se agregó TBME (30mL). El sólido blanco (390mg, 1,1mmol) formado se filtró para dar el producto crudo (390mg, 1,1mmol). El material se disolvió en DCM (20mL) y se calentó a 35°C durante diez minutos en la presencia de carbón vegetal (2g). La

suspensión se filtró a través de un tapón de celita, se lavó con DCM (20mL) y se concentró *en vacío* a 40°C para dar el compuesto del título como un sólido blanco (200mg, 36% de rendimiento) (pureza 97.3%).

^{1}H NMR [$(CD_3)_2SO$] δ 7,21 (d, *J* = 9,0 Hz, 1H), 7,00-7,06 (br s, 1H), 6,54 (d, *J* = 9,0 Hz, 1H), 5,55-5,59 (br s, 1H), 4,04 (m, 2H), 4,13 (m, 1H), 2,90 (dd, *J* = 3,8, 12,0 Hz, 1H), 2,80 (dd, *J* = 8,4, 12,0 Hz, 1H), 2,60 (m, 2H), 2,54 (s, 3H), 2,05-2,25 (br s, 2H), 1,70-1,88 (m, 5H), 1,48-1,63 (m, 2H), 1,25-1,38 (m, 1H).

Ejemplo 98

8'-Cloro-5'-[2-(etoxicarbonilmetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-$OCH_2CH_2NHCH_2COOCH_2CH_3$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una suspensión agitada del intermedio 8 (2,0g, 5,14mmol) en acetonitrilo (28mL) se agregó a una solución de glicinato de etilo (3,72g, 3,6mmol) en acetonitrilo (12mL). La mezcla se agitó bajo reflujo durante 24 horas. La concentración *en vacío* a 40°C dio un aceite naranja (5g) que se sometió a cromatografía de columna (sílice 110g, eluyendo con 50% a 100% EtOAc en heptano y luego 90% EtOAc en DCM) para dar el

compuesto del título (450mg, 22% de rendimiento) como un sólido blanco después de secar *en vacío* a 45°C.

^{1}H NMR [$(CD_3)_2SO$] δ 7,94-7,98 (br s, 1H), 7,24 (d, *J* = 9,0 Hz, 1H), 7,01-7,05 (br s, 1H), 6,62 (d, *J* = 9,0 Hz, 1H), 4,08 (t, *J* = 7,1 Hz, 2H), 4,01 (t, *J* = 5,6 Hz, 2H), 3,41 (s, 2H), 2,95 (t, *J* = 5,6 Hz, 2H), 2,45-2,55 (m, 2H), 2,12 (br s, 1H), 1,70-1,85 (m, 2H), 1,52-1,63 (m, 3H), 1,40-1,49 (m, 2H), 1,21-1,25 (m, 1H), 1,18 (t, *J* = 7,1 Hz, 3H).

Ejemplo 99

Clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona

X_1=C-$OCH_2CH_2NHCH_2COOH$, X_2=CH, X_3=CH, X_4=C-Cl, A=ciclohexilo, X=NH, Z=O, Y=NH

A una solución agitada del Ejemplo 98 (600mg, 1,52 mmol) en 1,4-dioxano (8mL) se agregó una solución de HCl (6N, 10,5mL) de 18°C a 20°C. La mezcla de la reacción se calentó a 90°C durante 2 h. Luego se enfrió sobre agua (100mL) y se lavó con DCM (200mL). La capa acuosa se concentró y se secó *en vacío* a 60°C para dar el compuesto del título (614mg, 99,9% de rendimiento) como un sólido blanco (pureza 95,9%).

^{1}H NMR (400 MHz, CD_3OD) δ 7,07 (d, *J* = 9,1 Hz, 1H), 6,56 (d, *J* = 9,1 Hz, 1H), 4,17 (t, *J* = 5,6 Hz, 2H), 3,86 (s, 2H), 3,39

(t, J = 5,6 Hz, 2H), 2,24-2,34 (m, 2H), 1,40-1,60 (m, 7H), 1,15-1,26 (m, 1H).

Resultados biológicos

Inhibición in vitro de la fosfodiesterasa 7 y de otras fosfodiesterasas

La capacidad de los compuesto de la invención de inhibir fosfodiesterasas nucleótidas cíclicas se evaluó midiendo su IC_{50} (concentración necesaria para inhibir la actividad enzimática un 50%).

PDE3A3, PDE4D3, PDE7A1 se clonaron y expresaron en células de insectos Sf21 usando el sistema de expresión de baculovirus y usamos directamente el sobrenadante del cultivo de células como la fuente de enzimas. La fuente de PDE1 y de PDE5 fueron cultivos de células humnas (respectivemente monocitos humanos TPH1 y adenocarcinoma de mamas caucásico humano MCF7).

Se obtuvieron parcialmente purificados sobre una columna de intercambio de aniones (Mono Q) de acuerdo con un método adaptado de Lavan B.E.,Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

Luego se hizo la medición de la actividad enzimática para diversos tipos de PDE de acuerdo con un método adaptado de W.J. Thompson et al. 1979, Avances en la Investigación de Nucleótidos Cíclicos, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY.

El sustrato usado fue cGMP para PDE1 y PDE5 y cAMP para PDE 3, PDE 4 y PDE 7. La concentración del sustrato fue de 0,2µM para PDE 1, PDE 3 y PDE 5, de 0,25µM para PDE 4 y de 50nM para PDE 7.

La reacción enzimática fue detenida después de 1 hora para PDE 1, PDE 3 y PDE 5 y de 10 minutos para PDE 4 y PDE 7.

Para determinar sus IC_{50}, los compuestos de la invención se ensayaron de 8 a 11 concentraciones en la gama de 0,02nM a 100µM para PDE 4 y PDE 7 y por lo menos a 6 concentraciones en la gama de 0,1µM a 30µM para PDE 1, 3 y 5.

La IC_{50} (µM) se determinó para algunos compuestos de la invención, y la IC_{50} de la mayor parte de los compuestos de los ejemplos 1 a 99 estuvo comprendida entre 0,008 µM y 18 µM.

La actividad de algunos de los compuestos más activos se resume en la siguiente tabla:

Ejemplo número	IC_{50} PDE7 (μM)
15	0,014
26	0,016
34	0,012
38	0,018
41	0,02
51	0,008
52	0,015
53	0,013
54	0,013

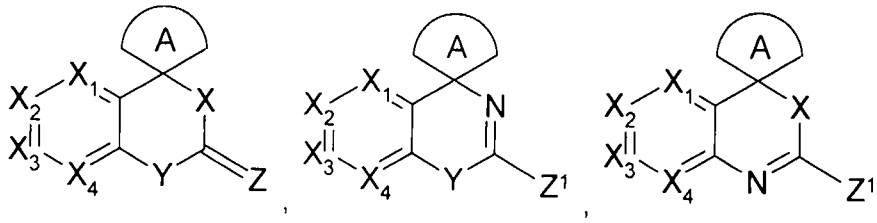
Estos resultados muestran que los compuestos de la invención inhiben PDE7 a muy bajas concentraciones, con algunos valores de IC_{50} inferiores a 100nM. Los resultados de los ensayos con otras PDE (1, 3, 4 y 5) muestran valores de IC_{50} frecuentemente superiores a 1μM o aún a 10 μM.

Esto demuestra que los compuestos de la invención son inhibidores resistentes y selectivos de PDE7.

REIVINDICACIONES

Habiendo descripto y determinado la naturaleza y alcance de la presente invención y la manera en que la misma ha de ser llevada a la práctica, se declara que lo que reivindica como invención y de propiedad exclusiva es:

1. Compuestos caracterizados porque tienen las fórmulas (I), (II) o (III):



(I) (II) (III)

en donde:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

$-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,

- alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o $=N-R^6$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

- R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H, $P(=O)(OH)_2$

- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2,

R se selecciona de hidrógeno, CN o SO_2NH_2 o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:

- hidrógeno,
- alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR', o NR'R" en donde R' y R" son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;
    - n es un número entero seleccionado de 0, 1, 2, 3 o 4;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, C(=O)-NH-SO_2-CH_3, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se

seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

  - $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3 y Q_5 es un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

  - un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de

    - H o

    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o

- cuando X_1 y X_2 ambos representan C-R^1, los 2 sustituyentes R^1 pueden formar junto con los átomos de carbono a los cuales están unidos, un anillo heterocíclico de 5 miembros que comprende un átomo de nitrógeno y optativamente un segundo heteroátomo seleccionado de O, S o N;

b) X es O o NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos compuestos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N,

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cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de $CH-NO_2$, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14}, $COOR^{10}$ o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, puden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior o

- cuando Y es $N-R^{12}$ y Z es $N-R^{13}$, pueden formar juntos un grupo -CH=N- o un grupo -C=C-,

- cuando X es $N-R^9$ y Z es $N-R^{13}$, R^9 y R^{13} pueden formar juntos un grupo -CH=N- o un grupo -C=C-;

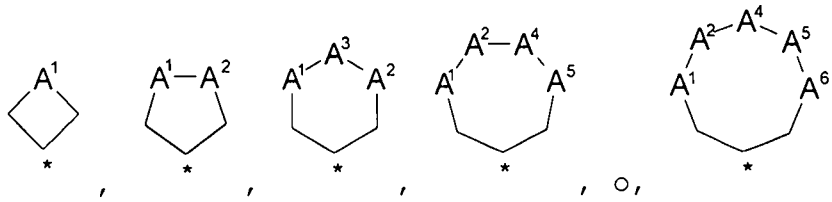
e) Z^1 se elige de H, CH_3 o $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14}, $COOR^{14}$ o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o más heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior;

f) A es un ciclo elegido de:



, , , , o,

en donde

- A^1, A^2, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,
  - alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;
  - A^3 se selecciona de O, S, C, C(=O), SO, SO_2 o N-R^{18} cuando A^1 y/o A^2 son C(=O) o cuando Y es O o S, en donde R^{18} es lo definido anteriormente;
- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes,

seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- 2 átomos del ciclo A, que no son adyacente, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que:

- no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;
- el ciclo A no contengan más de 2 átomos de carbono en un estado de hibridación sp^2;
- cuando X es O, X_2 no es $C-R^1$ en donde R^1 es
  - un tienilo sustituido con CN o con CN y CH_3,
  - un fenilo sustituido con CN, Cl, NO_2 o CN y F,
  - Br,
  - F;

o sus formas tautoméricas, sus formas racémicas o sus isómeros y sus derivados farmacéuticamente aceptables.

2. Un compuesto de la fórmula (II) o (III) de acuerdo con la reivindicación 1, caracterizado porque:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

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R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde
  - X^5 se selecciona de alquileno inferior o un solo enlace y
  - R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N, y pueden ser sustituidos con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y,

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos selecciondos de O, S o N;

b) X_4 es C-R^1 en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

e) Z^1 se elige de $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14}, o,

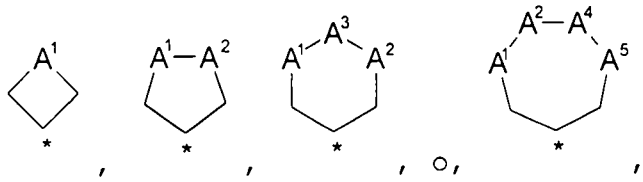
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- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14} o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior, y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N, y que pueden ser sustituidos con un alquilo inferior;

f) A es un ciclo elegido de:



, , , o, ,

en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:
  - un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes ,seleccionados de alquilo inferior, OH o F, o,
  - un átomo oxígeno;
- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono,

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siempre que:

no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representa un átomo de oxígeno.

3. Un compuesto de la fórmula (I), caracterizado porque X_1, X_2, X_3, X_4, X, Y, Z y A son lo definido en la reivindicación 1.

4. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 3, caracterizado porque:

a) X_1, X_2 y X_3 son iguales o diferentes y son C-R^1, en donde R^1 se selecciona de:

- hidrógeno, halógeno, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con halógeno, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ o $C(=O)NR^6R^7$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y

  R^6 y R^7, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de halógeno, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o

diferentes y se seleccionan de hidrógeno o alquilo inferior, y

R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;

- el grupo X^5-R^5 en donde
  - X^5 se selecciona de alquileno inferior o un solo enlace y
  - R^5 se selecciona de fenilo, piridilo o indolilo,

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3 en donde Q_3 se selecciona de:

- halógeno, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ o $C(=O)NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno, alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de halógeno, OR^6, $COOR^6$ o NR^6R^7 en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior y
  - R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno

o dos heteroátomos seleccionados de O, S o N, y pueden ser sustituidos con

- un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que pueden ser sustituidos con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y,

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos selecciondos de O, S o N;

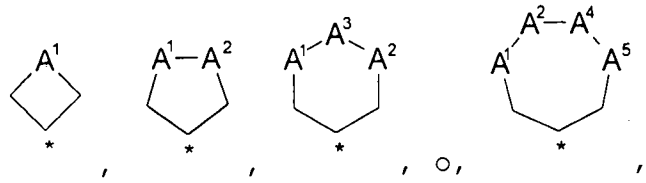
b) X_4 es C-R^1 en donde R^1 se selecciona de hidrógeno, halógeno, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$, $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) X es NH;

d) Y es NH;

e) Z^1 se elige de O, S o NR^{13} en donde R^{13} es hidrógeno o CN;

f) A es un ciclo elegido de:



en donde

- A^1, A^2, A^3, A^4 y A^5 son iguales o diferentes y se seleccionan de:
  - un átomo de carbono, no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes ,seleccionados de alquilo inferior, OH o F, o,
  - un átomo oxígeno;
- * representa el átomo de carbono que es compartido entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- 2 átomos del ciclo A, que no son adyacentes, pueden estar unidos por una cadena de 2, 3 o 4 átomos de carbono,

siempre que:

no más de uno de los grupos A^1, A^2, A^3, A^4 y A^5 simultáneamente representa un átomo de oxígeno.

5. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 1, caracterizado porque X_1, X_2, X_3 y X_4 son iguales o diferentes y son $-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos Q_2;

- el grupo X^5-R^5 en donde,

  - X^5 se selecciona de:

    - un solo enlace,

    - alquileno inferior, optativamente interrumpido con 1 heteroátomo elegidos de O, S y N,

  - R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H,

- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se

selecciona de hidrógeno o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:

- hidrógeno,
- alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
- Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con alquilo inferior, OR', o NR'R" en donde R' y R" son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;
- n es un número entero seleccionado de 0, 1, 2, 3 o 4;

estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos

seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que pueden contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

  - $(CH_2)_n$-Q_5, en donde n es un número entero de 0, 1, 2 y 3 y Q_5 es un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

  - un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de

    - H o

    - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N.

6. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 5, caracterizado porque X_1, X_2, X_3 y X_4 son iguales o diferentes y son $-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 átomos de flúor, OR^3, $COOR^3$ o NR^3R^4 en donde R^3 y R^4 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

  R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, pueden formar también un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N;
- el grupo X^5-R^5 en donde X^5 es un solo enlace y R^5 se selecciona de arilo, heteroarilo, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con 1, 2 o 3 grupos seleccionados de Q_3,

en donde Q_1 y Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, alquilo inferior,
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ o $SO_2NR^3R^4$ en donde R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior, $(CH_2)_n$-heteroarilo en donde n es un número entero seleccionado de 0, 1, 2 o 3;

estos grupos son no sustituidos o sustituidos con 1 o 2 grupos seleccionados de CN, SO_3H, OR^6, $COOR^6$ o NR^6R^7, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior, y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 6 miembros que puede contener uno o dos heteroátomos seleccionados de O o N, y que puede ser sustituido con

- un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N y que puede ser sustituido con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o,
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'', junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N.

7. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 5, caracterizado porque X_1 es C-R^1, en donde R^1 se selecciona de

- hidrógeno, halógeno, OR^2, COR^2, $COOR^2$, $CONR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de
- hidrógeno,
- alquilo inferior, Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, o N, o Q_4-cicloalquenilo optativamente sustituido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S o N, en donde
  - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior interrumpido con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior;
  - n es un número entero seleccionado de 0, 1, 2 o 3;

estos grupos son no sustituidos o sustituidos con CN, OR^6, SO_3H, $CONR^6R^7$, $COOR^6$, COR^6 o NR^6R^7,

en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, optativamente sustituido con NH_2, COOH, OH ;

R^6 y R^7 junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con

- $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o
- COR' o alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

- alquilo inferior optativamente sustituido con CN, SO_3H, OR^3, NR^3R^4, $COOR^3$ o $CONR^3R^4$ en donde R^3 y R^4 son iguales o diferentes y se seleccionan de
  - hidrógeno y
  - alquilo inferior optativamente sustituido con OH, COOH o NH_2
- el grupo X^5-R^5 en donde X^5 es un alquileno inferior optativamente interrumpido con un heteroátomo seleccionado de O y N y R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S o N y cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2, o 3 heteroátomos elegidos de O, S o N,

estos grupos son OR^3 o $COOR^3$ no sustituidos o sustituidos en donde R^3 se selecciona de hidrógeno y alquilo inferior;

R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 6 miembros, que puede contener uno o dos heteroátomos seleccionados de O o N, y que puede ser sustituido con

- $(CH_2)_n$-Q_5, en donde n es un número entero seleccionado de 0, 1, 2 y 3, y Q_5 es un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o
- C(=O)-R' o un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior.

8. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 5, caracterizado porque X_1 es C-R^1, en donde R^1 se selecciona de hidrógeno, halógeno o OR^2 en donde R^2 se selecciona de

- hidrógeno,
- alquilo inferior, no sustituido o sustituido con CN, OR^6, SO_3H, $COOR^6$ o NR^6R^7,
- $(CH_2)_n$-oxadiazol, $(CH_2)_n$-tetrazol , $(CH_2)_n$-morfolina, $(CH_2)_n$-furano, no sustituido o sustituido con OR^6 o $COOR^6$,

en donde n es 1 o 2 y R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, optativamente sustituido con NH_2 o COOH.

9. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5, 7 y 8, caracterizado porque X_2 es $C-R^1$, en donde R^1 es X^5-R^5, en donde

-X^5 es un solo enlace

-R^5 es fenilo o piridilo,

- optativamente sustituido con un alquilo inferior y
- sustituido con $C(=O)NR^3R^4$ en donde R^3 y R^4 junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

- un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o
- un alquilo inferior optativamente sustituido con OR', NR'R'', C(=O)NR'R'' o COOR' en donde R' y R'' son iguales o diferentes y se seleccionan de
  - H, o
  - alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R'' junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N.

10. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 9, caracterizado porque uno de X_1, X_2, X_3 y X_4 es C-R^1 en donde R^1 es hidrógeno mientras los otros son idénticos o diferentes y son C-R^1 en donde R^1 no es hidrógeno.

11. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 10, caracterizado porque X^3 es C-R^1 en donde R^1 es hidrógeno.

12. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 10, caracterizado porque X_3 es C-R^1, en donde R^1 se selecciona de:

- hidrógeno o halógeno, o
- X^5-R^5 en donde R^5 es un solo enlace y R^5 es arilo o heteroarilo, optativamente sustituido con uno, dos o tres grupos que son iguales o diferentes y que se seleccionan de halógeno, CN, CF_3, SO_2Me, OR^2, $COOR^2$, NR^2R^3, $SO_2NR^2R^3$ y $CONR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior.

13. Un compuesto de la fórmula (I) de acuerdo con la reivindicación 12, caracterizado porque X_3 es C-R^1, en donde R^1 se selecciona de hidrógeno o halógeno.

14. Un compuesto de la fórmula (I) de acuerdo con las reivindicaciones 5 a 13, caracterizado porque X_4 es C-R^1, en donde R^1 se selecciona de

- hidrógeno, halógeno, CF_3, O-alquilo inferior, $COOR^2$ o
- alquilo inferior optativamente sustituido con OR^2, $COOR^2$ o $SO_2NR^2R^3$ en donde R^2 y R^3 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior.

15. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 14, caracterizado porque X es NH.

16. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 15, caracterizado porque Y es NH.

17. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 16, caracterizado porque Z es O o N-CN.

18. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 17, caracterizado porque Z es O.

19. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 18, caracterizado porque A se selecciona de ciclohexilo o cicloheptilo, optativamente interrumpido con C(=O) o O, y no sustituido o sustituido con CH_3, OH o OCH_3.

20. Un compuesto de la fórmula (I) de acuerdo con cualquiera de las reivindicaciones 5 a 19, caracterizado porque A se selecciona de ciclohexilo o cicloheptilo no sustituido.

21. Un compuesto de la fórmula (I), (II) o (III) de acuerdo con cualquiera de las reivindicaciones 1 a 20, caracterizado porque cuando X_2 es $C\text{-}R^1$ y R^1 es $X^5\text{-}R^5$, entonces X^5 no es un solo enlace.

22. Un compuesto caracterizado porque se selecciona del grupo formado por:

Espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

Espiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

7'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona,

6'-Fenilespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

7'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-cloroespiro[ciclohexane-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-fluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6',7'-dicloroespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

5',6'-dicloroespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona,

8'-yodoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona,

8'-Bromoespiro[ciclobutano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona,

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-

2'(1'H)-ona,

8'-Bromo-4-metilespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[biciclo[3,2,1]octano-2-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

6',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona

8'-cloro-6'-yodoespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[cicloheptano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metilespiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-

dihidro)-quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-

dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(1H-indol-5il)espiro[ciclohexano-1-4'-(3',4'-

dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexano-

1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-

4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-metil-piperazin-1-

carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(3-N-dimetilamino-propilcarboxamido)fenil]-

espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-

ona,

8'-cloro-6'-[4-(2-N-dimetilamino-etilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro -6'-[3-(4-metil-piperazin-1-carbónil)-fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(2-N-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-tiona

8'-Cloro-2'-cianoiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina

8'-Cloro-2'-metoxiiminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina,

8'-Cloro-2'-dimetilaminoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolina],

8'-Cloro-1'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-1'-(etoxicarbonilmetil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-Cloro-3'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-imidazo[2,1-b]quinazolina

9'-Cloroespiro[ciclohexano-1-5'-(5',10'-dihidro)]-[1,2,4]triazolo[3,4-b]quinazolina,

9'-Cloroespiro[ciclohexano-1-5'-(4',5'-dihidro)]-[1,2,4]triazolo[4,3-a]quinazolina,

Espiro[ciclohexano-1-9'-(8',9'-dihidro)-pirazolo[4',3'-f]quinazolin]-7'(6'H)-ona,

8'-Cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-one,

5',8'-difluoroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-(morfolin-4-il)metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxi-6'-yodo-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-yodo-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-dimetilaminoetoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-aminoetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(metilamino)etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(2-aminoetoxi)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[3-dimetilaminopropoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-etoxicarbonilmetoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxmetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxipropoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-(3-sulfopropoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(tetrahidro-piran-2-iloxi)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-etoxicarbonil-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexane-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-yodo-5'-[2-dimetilamino-etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifhenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-metoxi-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8-Cloro-5-metoxiespiro[4H-benzo[d][1,3]oxazin-2-ilamino-4-4'-(tetrahidro-piran-4'-ilo)],

8'-Trifluorometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-cianometilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-dimetilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(3-metilamino-2-hidroxi-propoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(etoxicarbonilmetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

Clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona.

23. Un compuesto caracterizado porque se selecciona del grupo formado por:

8'-bromoespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5',8'-dicloroespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Bromoespiro[cicloheptano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-fenilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(4-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloroespiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(1H-indol-5il)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(2-piridil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-dimetilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)-quinazolin]-2'(1'H)-ona,

8'-cloro-6'-(3-metilamino-prop-1-inil)espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(2-N-dimetilamino-etilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[3-(3-N-dimetilamino-propilcarboxamido)fenil]-espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro -6'-[3-(4-metil-piperazin-1-carbonil)-fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ons,

8'-cloro-6'-[3-(2-N-dimetilamino-etilcarboxamido)fenil]espiro-[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-pirimidin-2-il-piperazin-1-carbonil)fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-

dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-morfolin-4-il-2-oxo-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(4-(2-hidroxi-etoxi)-etil)-piperazin-1-carbonil)-fenil]espiro[-ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-metilespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-hidroxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-6'-ciano-5'-metoxi-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-[2-(4-morfolino)etoxi]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboximetoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

5'-carboxipropoxi-8'-cloro-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-5'-(3-sulfopropoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(2-hidroxi-etoxi)-espiro[ciclohexano-1-4'-

(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-etoxicarbonil-furan-2-ilmetoxy)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-carboxi-furan-2-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-cianometoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(1H-tetrazol-5-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-Cloro-5'-(5-hidroxi-[1,2,4]oxadiazol-3-ilmetoxi)-espiro[ciclohexano-1-4'-(3',4'-dihidro) quinazolin]-2'(1'H)-ona,

6'-(4-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

6'-(3-carboxifenil)-8'-cloro-5'-metoxiespiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[2-metil-4-(4-metil-piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

8'-cloro-6'-[4-(piperazin-1-carbonil)fenil]espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona,

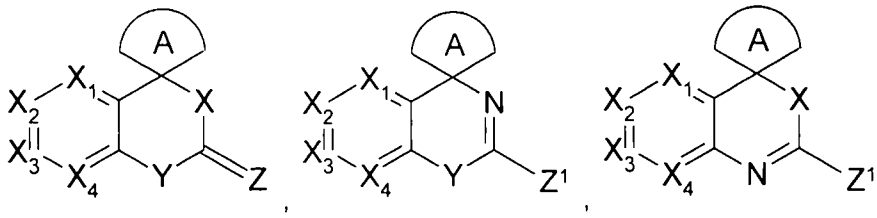
8'-cloro-6'-[4-carbamoil-fenil]espiro[ciclohexano-1-4'-

(3',4'-dihidro)quinazolin]-2'(1'H)-ona,
8'-cloro-6'-[4-((1-metil-piperidin-4-il)-piperazin-1-carbonil)fenil] espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona, y
Clorhidrato de 8'-Cloro-5'-[2-(carboximetil-amino)-etoxi]-espiro[ciclohexano-1-4'-(3',4'-dihidro)quinazolin]-2'(1'H)-ona.

24. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 23, caracterizado por su uso como un medicamento.

25. Una composición farmacéutica, caracterizada porque comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 23 en combinación con un portador apropiado.

26. El uso de un compuesto de la fórmula (I), (II) o (III)



(I) (II) (III)

caracterizado porque:

a) X_1, X_2, X_3 y X_4 son iguales o diferentes y se seleccionan de:

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- N, siempre que no más de dos de los grupos X_1, X_2, X_3 y X_4 representen simultáneamente un átomo de nitrógeno, o

$-C-R^1$, en donde R^1 se selecciona de:

- Q_1, o
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con uno o varios grupos Q_2;
- el grupo X^5-R^5 en donde,
  - X^5 se selecciona de:
    - un solo enlace,
    - alquileno inferior, alquenileno inferior o alquinileno inferior, optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, los átomos de carbono de estos grupos son no sustituidos o sustituidos con uno o varios grupos, idénticos o diferentes, seleccionados de SR^6, OR^6, NR^6R^7, =O, =S, o $=N-R^6$ en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior, y
  - R^5 se selecciona de arilo, heteroarilo, cicloalquilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con C(=O) o con 1, 2 o 3 heteroátomos elegidos de O,

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S, S(=O), SO_2 o N, o un grupo bicíclico, estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de Q_3, heteroarilo o alquilo inferior optativamente sustituido con Q_3;

en donde Q_1, Q_2, Q_3 son iguales o diferentes y se seleccionan de

- hidrógeno, halógeno, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ o NR^3-Q-R^2 en donde Q se selecciona de C(=NR), C(=O), C(=S) o SO_2, R se selecciona de hidrógeno, CN o SO_2NH_2 o alquilo inferior y R^2, R^3 y R^4 son iguales o diferentes y se seleccionan de:
  - hidrógeno,
  - alquilo inferior optativamente interrumpido con C(=O), Q_4-arilo, Q_4-heteroarilo, Q_4-cicloalquilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, o Q_4-cicloalquenilo optativamente interrumpido con C(=O) o con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, en donde
    - Q_4 se selecciona de $(CH_2)_n$, alquilo inferior con un heteroátomo seleccionado de O, S o N, alquenilo inferior o alquinilo inferior, estos grupos son optativamente sustituidos con

alquilo inferior, OR', o NR'R" en donde R' y R" son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

- n es un número entero seleccionado de 0, 1, 2, 3 o 4;

estos grupos son no sustituidos o sustituidos con uno o varios grupos seleccionados de halógeno, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)-NH-SO_2-CH_3$, CF_3, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ o $SO_2NR^6R^7$, en donde R^6 y R^7 son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con uno o dos grupos seleccionados de OR, COOR, o NRR^8 en donde R y R^8 son hidrógeno o alquilo inferior y

- R^6 y R^7, y/o, R^3 y R^4, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S, S(=O), SO_2 o N, y que puede ser sustituido con

- $(CH_2)_n-Q_5$, en donde n es un número entero seleccionado de 0, 1, 2 y 3 y Q_5 es un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N y que puede ser sustituido con un alquilo inferior o,

- un alquilo inferior optativamente sustituido con OR', NR'R", C(=O)NR'R" o COOR' en donde R' y R" son iguales o diferentes y se seleccionan de

- H o

- alquilo inferior optativamente sustituido con OR o COOR en donde R es hidrógeno o alquilo inferior y

R' y R" junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros, que puede contener uno o dos heteroátomos seleccionados de O, S o N; o

- cuando X_1 y X_2 ambos representan C-R^1, los 2 sustituyentes R^1 pueden formar junto con los átomos de carbono a los cuales están unidos, un anillo heterocíclico de 5 miembros que comprende un átomo de nitrógeno y optativamente un segundo heteroátomo seleccionado de O, S o N;

b) X es O, S o NR^9, en donde R^9 se selecciona de

- hidrógeno, CN, OH, NH_2,

- alquilo inferior, alquenilo inferior o alquinilo inferior, estos compuestos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son

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iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

c) Y se selecciona de O, S o N-R^{12}, en donde R^{12} se selecciona de:

- hidrógeno, CN, OH, NH_2,
- alquilo inferior, alquenilo inferior o alquinilo inferior, estos grupos son no sustituidos o sustituidos con cicloalquilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con 1 o 2 heteroátomos elegidos de O, S, S(=O), SO_2 o N, arilo, heteroarilo, OR^{10}, $COOR^{10}$ o $NR^{10}R^{11}$ en donde R^{10} y R^{11} son iguales o diferentes y se seleccionan de hidrógeno o alquilo inferior;

d) Z se elige de CH-NO_2, O, S o NR^{13} en donde R^{13} se selecciona de:

- hidrógeno, CN, OH, NH_2, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,

- alquilo inferior, no sustituido o sustituido con uno o varios grupos que son iguales o diferentes y que se seleccionan de OR^{14}, $COOR^{10}$ o $NR^{14}R^{15}$;

R^{14} y R^{15} se seleccionan independientemente de hidrógeno o alquilo inferior, o, R^{14} y R^{15}, junto con el átomo de nitrógeno al cual están unidos, puden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o dos heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior o

- cuando Y es $N-R^{12}$ y Z es $N-R^{13}$, pueden formar juntos un grupo -CH=N- o un grupo -C=C-,
- cuando X es $N-R^{9}$ y Z es $N-R^{13}$, R^{9} y R^{13} pueden formar juntos un grupo -CH=N- o un grupo -C=C-;

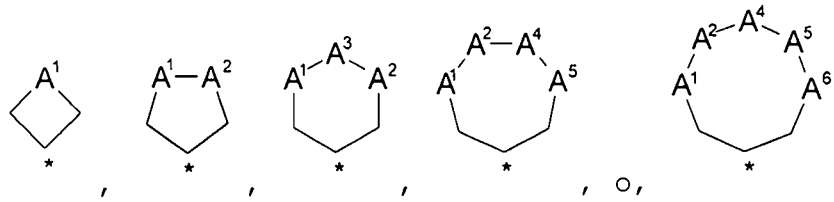
e) Z^1 se elige de H, CH_3 o $NR^{16}R^{17}$ en donde R^{16} y R^{17} son iguales o diferentes y se seleccionan de:

- hidrógeno, CN, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, o,
- alquilo inferior no sustituido o sustituido con uno o varios grupos seleccionados de OR^{14}, $COOR^{14}$ o $NR^{14}R^{15}$,

R^{14} y R^{15} se eligen de hidrógeno o alquilo inferior y

R^{14} y R^{15}, y/o, R^{16} y R^{17}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros que puede contener uno o más heteroátomos elegidos de O, S o N, y que puede ser sustituido con un alquilo inferior;

f) A es un ciclo elegido de:



, , , , o,

en donde

- A^i, A^2, A^3, A^4, A^5 y A^6 son iguales o diferentes y se seleccionan de O, S, C, C(=O), SO, SO_2 o N-R^{18} en donde R^{18} se selecciona de:
  - hidrógeno, arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpidos con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N,
  - alquilo inferior no sustituido o sustituido con arilo, heteroarilo, cicloalquilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, cicloalquenilo optativamente interrumpido con uno o varios heteroátomos elegidos de O, S, S(=O), SO_2 o N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ o $C(=O)OR^{19}$

en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior;

- * representa el átomo de carbono que se comparte entre el ciclo A y el ciclo de la cadena principal que contiene X y/o Y;
- cada átomo de carbono del ciclo A es no sustituido o sustituido con 1 o 2 grupos, idénticos o diferentes, seleccionados de alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$, haloalquilo inferior, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ o $NR^{19}R^{20}$ en donde R^{19} y R^{20} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior optativamente sustituido con OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ o $CONR^{21}R^{22}$ en donde R^{21} y R^{22} son idénticos o diferentes y se seleccionan de hidrógeno o alquilo inferior, y
  R^{19} y R^{20}, y/o, R^{21} y R^{22}, junto con el átomo de nitrógeno al cual están unidos, pueden formar un anillo heterocíclico de 4 a 8 miembros;
- 2 átomos del ciclo A, que no son adyacente, pueden ser unidos por una cadena de 2, 3 o 4 átomos de carbono que puede ser interrumpida con 1 heteroátomo elegido de O, S o N;

siempre que no más de dos de los grupos A^1, A^2, A^3, A^4, A^5 y A^6 simultáneamente representen un heteroátomo;

o sus formas tautoméricas, sus formas racémicas o sus isómeros y

sus derivados farmacéuticamente aceptables,
para la preparación de un medicamento para la prevención o el tratamiento de trastornos para los cuales la tarapia con un inhibidor de PDE7 es relevante.

27. El uso de acuerdo con la reivindicación 26, caracterizado porque dicho compuesto es un compuesto de la fórmula (I) en donde X_1, X_2, X_3, X_4, X, Y, Z y A son lo definido en la reivindicación 25.

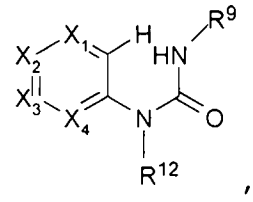
28. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 23, caracterizado por la preparación de un medicamento para la prevención o el tratamiento de desórdenes para los cuales la terapia con un inhibidor de PDE7 es relevante.

29. El uso de acuerdo con cualquiera de las reivindicaciones 26 a 28, caracterizado porque el trastorno se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica, asma, cáncer, síndrome de inmunodeficiencia adquirida, alergia o enfermedad intestinal inflamatoria.

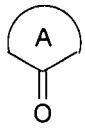
30. Un método para la prevención o el tratamiento de un trastorno para el cual la terapia con un inhibidor de PDE7 es relevante, caracterizado porque comprende administrar a un mamífero que lo necesita, una cantidad efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 23.

31. Un método de acuerdo con la reivindicación 30, caracterizado porque el trastorno se selecciona de enfermedades relacionadas con las células T, enfermedades autoinmunes, osteoartritis, esclerosis múltiple, enfermedad pulmonar obstructiva crónica, asma, cáncer, síndrome de inmunodeficiencia adquirida, alergia o enfermedad intestinal inflamatoria.

32. Un método para preparar un compuesto de la fórmula (I) de acuerdo con la reivindicación 1 en donde Y es $N\text{-}R^{12}$, X es $N\text{-}R^{9}$ y Z es O, caracterizado porque comprende hacer reaccionar una urea sustituida de la fórmula



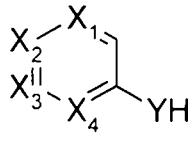
en donde X_1, X_2, X_3, X_4, R_9 y R_{12} son lo definido en la reivindicación 1, con una cetona cíclica de la fórmula



en donde A es lo definido en la reivindicación 1, para obtener un compuesto de la fórmula (I) y aislar dicho compuesto de la fórmula (I).

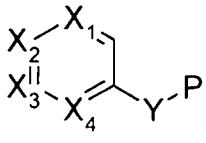
33. Un método para preparar un compuesto de la fórmula (I) de acuerdo con la reivindicación 1 en donde X_1, X_2, X_3, X_4, A y R^9 son lo definido en la reivindicación 1 e Y es O, S o NH, dicho método caracterizado porque comprende:

(1) hacer reaccionar un compuesto (2a)



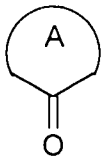
(2a)

en donde X_1, X_2, X_3, X_4 son lo definido en la reivindicación 1 e Y es O, S o NH, con un grupo P-LG en donde P es un grupo protector y LG es un grupo saliente para obtener el compuesto (2b)

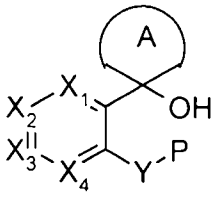


(2b)

(2) hacer reaccionar el compuesto (2b) con R-Li en donde R es alquilo inferior y luego con una cetona de la fórmula

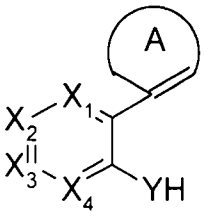


en donde A es lo definido en la reivindicación 1 para obtener el compuesto (2c)



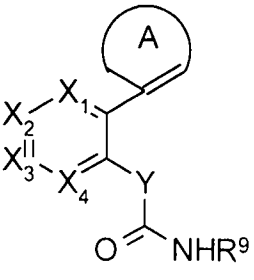
(2c)

(3) remoer el grupo protector P en condiciones reductoras, en condiciones ácidas o en condiciones básicas para obtener el compuesto (2d)



(2d)

(4) hacer reaccionar el compuesto (2d) con un grupo $O=C=N-R^9$ en donde R^9 es lo definido en la reivindicación 1 para obtener el compuesto (2e)



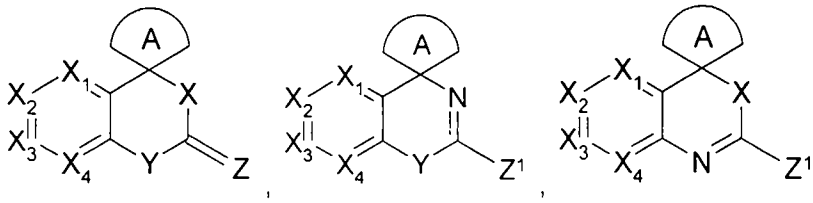
(2e)

(5) hacer reaccionar el compuesto (2e) con un ácido para obtener dicho compuesto de la fórmula (I),

(6) aislar el compuesto de la fórmula (I).

RESUMEN DE LA INVENCIÓN

La invención provee compuestos que son inhibidores de PDE7, que tienen las siguientes fórmulas (I), (II) y (III)



(I) (II) (III)

en donde X_1, X_2, X_3, X_4, X, Y, Z, A y Z^1 son lo definido en la memoria descriptiva, métodos para prepararlos y su uso para el tratamiento de trastornos para los cuales la terapia con un inhibidor de PDE7 es relevante.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
018318 (A475) TP		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP02/03594	18/03/2002	21/03/2001
International Patent Classification (IPC) or national classification and IPC C07D239/70		
Applicant WARNER-LAMBERT COMPANY et al.		

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 6 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 35 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - 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 Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting 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
11/10/2002	23.05.2003
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 Mathys, E Telephone No. +49 89 2399 8596

Form PCT/IPEA/409 (cover sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP02/03594

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:

1-149	as originally filed				

Claims, No.:

1-33	as received on	25/02/2003	with letter of	21/02/2003	

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.)

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. 30,31.

because:

☒ the said international application, or the said claims Nos. 30,31 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	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-29,32,33

No: Claims

2. Citations and explanations
see separate sheet

ITEM III

Claims 30 and 31 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 (see Article 34(4)(a)(i) PCT, cf. also ITEM V).

ITEM V

Novelty

Present compounds (cf. e.g. formula (II) in case Y = NH and $Z^1 = NH_2$) differ from those disclosed by (D1) WO-A-97/14686 in the position of the spiro-cyclo, from compounds disclosed by (D2)WO-A-00/66560 by having the hetero part of the condensed saturated. (D3) JOURNAL OF THE CHEMICAL SOCIETY, vol. 8, 1984, pages 1863-8 does not disclosed any spirocycles.

Inventive Step

Present compounds (cf. e.g. formula (II) in case Y = NH and $Z^1 = NH_2$) substantially only differ from such ones useful in the treatment of the same disorders disclosed by D1 (see e.g. claim 10 and page 34) in the position of the spiro cycle.
This variation is considered an obvious measure to solve the problem of providing alternatives to the known compounds (the expectation could be verified with a few routine tests), all the more so as D2 already discloses the present position for similar compounds i.a. also being (as the present ones) useful in the treatment of cancers (cf. e.g. claim 20 with present claim 29 (last indication on line 26 on page 32)). The high degree of predictability thought possible in this field is illustrated by the Applicant himself by the extremely broad scope regarding e.g. the spirocycles without adequate support by specific activity data for a representative number of compounds, which generalisations refute the statement that minor structural variations were expected to cause a loss of activity of the modified compound.
Accordingly, the present subject matter does not fulfil the requirements of Article 33(3) of the PCT.

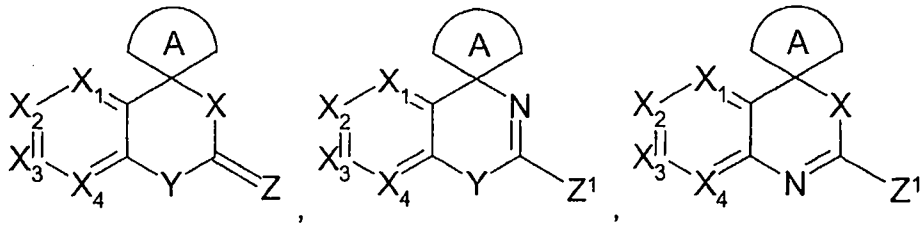
The above obviousness objection could be overcome if it were shown that the present compounds exhibit unexpected properties (i.e. unexpectedly solve a problem not yet solved) when compared to compounds according to the above mentioned state of the art being identical except for the above mentioned difference.
It is pointed out in this context that only therapeutic effects (and not an alleged different mechanism) can be relevant in establishing an inventive step and that a therapeutic effect eventually establishing an inventive step should extend to the whole of the scope claimed.

Industrial Applicability

For the assessment of present claims 30 and 31 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 (as present claim 28).

Claims

1. Compounds having the following formula (I), (II) or (III),



(I) (II) (III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, , the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)-NH-SO_2-CH_3$, NR^3R^4, $Q-R^2$, $Q-NR^3R^4$, $NR^2-Q-NR^3R^4$ or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;

  these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, $C(=O)-NH-SO_2-CH_3$, CF_3, OR^6, $COOR_6$, $C(=O)R^6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2, or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one

or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{10}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is N-R^{12} and Z is N-R^{13}, may form together a -CH=N- group or a -C=C- group,
- when X is N-R^9 and Z is N-R^{13}, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

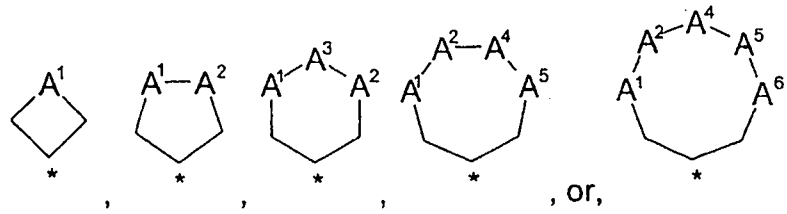
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, or,

in which,

- A^1, A^2, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:
  - hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
  - lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- A^3 is selected from O, S, C, C(=O), SO or SO_2, or N-R^{18} when A^1 and/or A^2 are C(=O) or when Y is O or S, wherein R^{18} is as defined above;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,

  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that:

- not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;
- the cycle A does not contain more than 2 carbon atoms in an sp^2 hybridization state;
- when X is O, X_2 is not C-R^1 in which R^1 is
  - a thienyl substituted with CN or with CN and CH_3,
  - a phenyl substituted with CN, Cl, NO_2 or CN and F,
  - Br
  - F;

or their tautomeric forms, their racemic forms or their isomers and their pharmaceutically acceptable derivatives,

it being understood that,

lower alkyl and lower alkylene denote straight and branched carbon chains having from 1 to 6 carbon atoms;

lower alkenyl and lower alkenylene denote straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one double bond;

lower alkynyl and lower alkynylene denote straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one triple bond;

lower haloalkyl includes a lower alkyl as defined above, substituted with one or several halogens;

aryl refer to an aromatic carbocycle containing between 6 and 10 carbon atoms;

heteroaryl denote an aromatic cycle which have from 5 to 10 ring atoms, from 1 to 4 of which are independently selected from the group consisting of O, S, and N;

heterocyclic ring include heteroaryl as defined above and cycloalkyl or cycloalkenyl interrupted with 1, 2 or 3 heteroatoms chosen from O, S, S(=O), SO_2, or N;

bicyclic group denotes two cycles, which are the same or different and which are chosen from aryl, heterocyclic ring, cycloalkyl or cycloalkenyl, fused together to form said bicyclic group.

2. A compound of formula (II) or (III) according to claim 1, in which,

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, SO_3H, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:
  - halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, NH-$C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
    - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in

which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

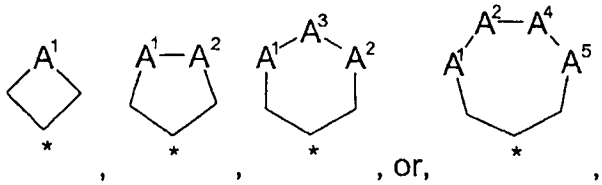
e) Z^1 is chosen from $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, $C(=O)R^{14}$, $(C=O)NR^{14}R^{15}$, OR^{14},
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14} or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

3. A compound of formula (I) in which X_1, X_2, X_3, X_4, X, Y, Z and A are as defined in claim 1.

4. A compound of formula (I) according to claim 3 in which

a) X_1, X_2 and X_3 are the same or different and are C-R^1, in which R^1 is selected from:

- hydrogen, halogen, CN, SO_3H, NO_2, CF_3, OR^2, SR^2, NR^2R^3, COR^2, $COOR^2$, $CONR^2R^3$, SO_2CH_3, $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR^6, $COOR^6$, NR^6R^7, $SO_2NR^6R^7$ or $C(=O)NR^6R^7$ in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^6 and R^7, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO_3H, OR^2, $COOR^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl, and,

  R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

- the group X^5-R^5 in which,
  - X^5 is selected from a lower alkylene or a single bond, and,
  - R^5 is selected from phenyl, pyridyl or indolyl,

  these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3 in which Q3 is selected from:
  - halogen, CN, SO_3H, NO_2, CF_3, OR^2, $OC(=O)R^2$, $C(=O)R^2$, $C(=O)OR^2$, $NH\text{-}C(=O)R^2$, NR^3R^4, $SO_2NR^3R^4$ or $C(=O)NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
    - hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR^6, $COOR^6$ or NR^6R^7 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl and,
    - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with,
      - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
      - a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from,
        - H, or,
        - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

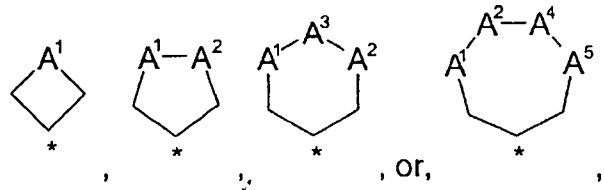
b) X_4 is C-R^1 in which R^1 is selected from hydrogen, halogen, CN, NO_2, SO_2CH_3, SO_3H, CH_3, CF_3, OR^2, SR^2, NR^2R^3, $COOR^2$, $CONR^2R^3$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl;

c) X is NH;

d) Y is NH;

e) Z is chosen from O, S or NR^{13} in which R^{13} is hydrogen or CN;

f) A is a cycle chosen from:



, , , or, ,

in which,

- A^1, A^2, A^3, A^4 and A^5 are the same or different and are selected from:
  - a carbon atom, unsubstituted or substituted with 1 or 2 groups, identical or different ,selected from lower alkyl, OH or F, or,
  - an oxygen atom;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain;

provided that:

- not more than one of the groups A^1, A^2, A^3, A^4 and A^5 simultaneously represent an oxygen atom.

5. A compound of formula (I), according to claim 1 in which, X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X^5-R^5 in which,

- X^5 is selected from :
  - a single bond,
  - a lower alkylene, optionally interrupted with 1 heteroatoms chosen from O, S and N
- R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H,
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, $C(=O)\text{-}NH\text{-}SO_2\text{-}CH_3$, NR^3R^4, $Q\text{-}R^2$, $Q\text{-}NR^3R^4$, $NR^2\text{-}Q\text{-}NR^3R^4$ or $NR^3\text{-}Q\text{-}R^2$ in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;
  - these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH_3, SO_3H, SO_2CH_3, CF_3, $C(=O)NH\text{-}SO_2CH_3$, OR^6, $COOR^6$, $C(=O)R^6$, NR^6R^7, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are

selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

6. A compound of formula (I) according to claim 5, in which X_1, X_2, X_3 and X_4 are the same or different and are C-R^1, in which R^1 is selected from:

- Q1, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 fluor atoms, OR^3, $COOR^3$ or NR^3R^4 in which R^3 and R^4 are the same or different and are selected from hydrogen or lower alkyl;

  R^3 and R^4 together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;

- the group X^5-R^5 in which X^5 is a single bond and R^5 is selected from aryl, heteroaryl, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3,

in which Q1 and Q3 are the same or different and are selected from

- hydrogen, halogen, CN, lower alkyl,
- OR^2, $C(=O)OR^2$, NR^3R^4, $C(=O)NR^3R^4$ or $SO_2NR^3R^4$ in which R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl, Q4-heteroaryl in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 0, 1, 2 or 3;
    these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO_3H, $C(=O)$-NH-SO_2-CH_3, OR^6, $COOR^6$ or NR^6R^7, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,
  - R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,
- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R'' together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

7. A compound of formula (I) according to claim 5, in which, X_1 is C-R^1, in which R^1 is selected from

- hydrogen, halogen, OR^2, COR^2, $COOR^2$,$CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from
  - hydrogen,
  - lower alkyl, Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, in which
    - Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl;
    - n is an integer selected from 0, 1, 2 or 3;

  these groups being unsubstituted or substituted with lower alkyl, CN, OR^6, SO_3H, C(=O)-NH-SO_2-CH_3, $CONR^6R^7$, $COOR^6$, COR^6 or NR^6R^7,
  in which and R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2, COOH, OH ;
  R^6 and R^7 together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with ,
    - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
    - COR' or lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from hydrogen or lower alkyl;

- lower alkyl optionally substituted with CN, SO_3H, OR^3, NR^3R^4, $COOR^3$ or $CONR^3R^4$ in which R^3 and R^4 are the same or different and are selected from
  - hydrogen and,
  - lower alkyl optionally substituted with OH, COOH or NH_2

- the group X^5-R^5 in which X^5 is a lower alkylene optionally interrupted with a heteroatom selected from O and N and R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N and cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N,

these groups being unsubstituted or substituted OR^3 or $COOR^3$ in which R^3 is selected from hydrogen and lower alkyl;

R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- C(=O)-R' or a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from hydrogen or lower alkyl.

8. A compound of formula (I) according to claim 5 in which, X_1 is C-R^1, in which R^1 is selected from hydrogen, halogen or OR^2 in which R^2 is selected from

- hydrogen,
- lower alkyl, unsubstituted or substituted with CN, C(=O)-NH-SO_2-CH_3, OR^6, SO_3H, $COOR^6$ or NR^6R^7;
- Q4-oxadiazole, Q4-tetrazole, Q4-morpholine, Q4-furan, Q4-isoxazole, in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and $(CH_2)_n$ in which n is an integer selected from 1 and 2;

these groups being unsubstituted or substituted with CH_3, OR^6 or $COOR^6$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2 or COOH.

9. A compound of formula (I) according to any one of claims 5, 7 and 8 in which X_2 is C-R^1, in which R^1 is X^5-R^5, in which

- X^5 is a single bond,
- R^5 is phenyl or pyridyl,
  - optionally substituted with a lower alkyl, and,
  - substituted with $C(=O)NR^3R^4$ in which R^3 and R^4 together with the nitrogen atom to which they are linked, form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

  R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

10. A compound of formula (I) according to any one of claims 5 to 9 in which one of X_1, X_2, X_3 and X_4 is $C\text{-}R^1$ in which R^1 is hydrogen while the others are identical or different and are $C\text{-}R^1$ in which R^1 is other than hydrogen.

11. A compound of formula (I) according to claim 10, in which X^3 is $C\text{-}R^1$ in which R^1 is hydrogen.

12. A compound of formula (I) according to any one of claims 5 to 10, in which X_3 is $C\text{-}R^1$, in which R^1 is selected from :

- hydrogen or halogen, or,
- $X^5\text{-}R^5$ in which R^5 is a single bond and R^5 is aryl or heteroaryl, optionally substituted with one, two or three groups which are the same or different and which are selected from halogen, CN, CF_3, SO_2Me, OR^2, $COOR^2$,

NR^2R^3, $SO_2NR^2R^3$ and $CONR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl.

13. A compound of formula (I) according to claim 12 in which X_3 is C-R^1, in which R^1 is selected from hydrogen or halogen.

14. A compound of formula (I) according to any one of claims 5 to 13 in which X_4 is C-R^1, in which R^1 is selected from
- hydrogen, halogen, CF_3, O-lower alkyl, $COOR^2$ or,
- lower alkyl optionally substituted with OR^2, $COOR^2$ or $SO_2NR^2R^3$ in which R^2 and R^3 are the same or different and are selected from hydrogen or lower alkyl.

15. A compound of formula (I) according to any one of claims 5 to 14 in which X is NH.

16. A compound of formula (I) according to any one of claims 5 to 15 in which Y is NH.

17. A compound of formula (I) according to any one of claims 5 to 16 in which Z is O or N-CN.

18. A compound of formula (I) according to any one of claims 17 in which Z is O.

19. A compound of formula (I) according to any one of claims 5 to 18 in which A is selected from cyclohexyl or cycloheptyl, optionally interrupted with C(=O) or O, and unsubstituted or substituted with CH_3, OH or OCH_3.

20. A compound of formula (I) according to any one of claims 5 to 19 in which A is selected from unsubstituted cyclohexyl or cycloheptyl.

21. A compound of formula (I), (II) or (III) according to any one of claims 1 to 20 wherein when X_2 is C-R^1 and R^1 is X^5-R^5, then X^5 is not a single bond

22. A compound selected from the group consisting of
Spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
Spiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
7'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',7'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',6'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cyclobutane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinàzolin]-2'(1'H)-one,
8'-Bromo-4-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one
8'-chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-thione
8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline
8'-Chloro-2'-methoxyiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline,
8'-Chloro-2'-dimethylaminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline],
8'-Chloro-1'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-1'-(ethoxycarbonylmethyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,

8'-Chloro-3'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-imidazo[2,1-b]quinazoline
9'-Chlorospiro[cyclohexane-1-5'-(5',10'-dihydro)]-[1,2,4]triazolo[3,4-b]quinazoline,
9'-Chlorospiro[cyclohexane-1-5'-(4',5'-dihydro)]-[1,2,4]triazolo[4,3-a]quinazoline,
Spiro[cyclohexane-1-9'-(8',9'-dihydro)-pyrazolo[4',3'-f]quinazolin]-7'(6'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-aminoethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8-Chloro-5-methoxyspiro[4H-benzo[d][1,3]oxazin-2-ylamine-4-4'-(tetrahydro-pyran-4'-yl)],
8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(ethoxycarbonylmethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

23. A compound selected from the group consisting of
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)–quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]–spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro -6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro–[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[–cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2'(1'H)-one,

6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl] spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, and,

8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride,

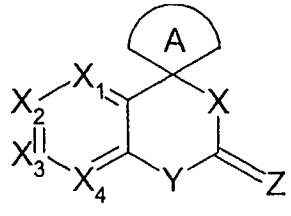
8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

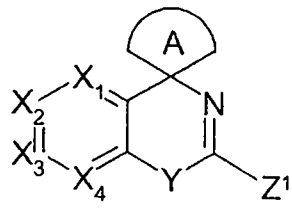
24. A compound according to any one of claim 1 to 23 for use as a medicament

25. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23 in combination with an appropriate carrier.

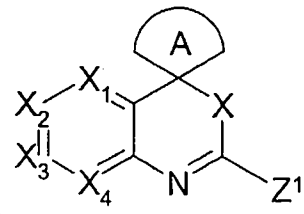
26. Use of a compound of formula (I), (II) or (III),



(I)



(II)



(III)

in which,

a) X_1, X_2, X_3 and X_4 are the same or different and are selected from:

- N, provided that not more than two of the groups X_1, X_2, X_3 and X_4 simultaneously represent a nitrogen atom, or,
- C-R^1, in which R^1 is selected from:
  - Q1, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q2;
  - the group X^5-R^5 in which,
    - X^5 is selected from :
      - a single bond,
      - lower alkylene, lower alkenylene or lower alkynylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR^6, OR^6, NR^6R^7, =O, =S or =N-R^6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, and,
    - R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO_2 or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q1, Q2, Q3 are the same or different and are selected from

- hydrogen, halogen, CN, NO_2, SO_3H, $P(=O)(OH)_2$
- OR^2, $OC(=O)R^2$, $C(=O)OR^2$, SR^2, $S(=O)R^2$, C(=O)-NH-SO_2-CH_3, NR^3R^4, Q-R^2, Q-NR^3R^4, NR^2-Q-NR^3R^4 or NR^3-Q-R^2 in which Q is selected from C(=NR), C(=O), C(=S) or SO_2, R is selected from hydrogen, CN, SO_2NH_2 or lower alkyl and R^2, R^3 and R^4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2

heteroatoms chosen from O, S, S(=O), SO_2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, in which

- Q4 is selected from $(CH_2)_n$, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R'' in which R' and R'' are the same or different and are selected from hydrogen or lower alkyl;
- n is an integer selected from 0, 1, 2, 3 or 4;

these groups being unsubstituted or substituted with one or several groups selected from halogen, lower alkyl, CN, CH_3, SO_3H, SO_2CH_3, C(=O)-NH-SO_2-CH_3, CF_3, OR^6, $COOR_6$, $C(=O)R_6$, NR^6R^7, $NR^6C(=O)R^7$, $C(=O)NR^6R^7$ or $SO_2NR^6R^7$, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR^8 in which R and R^8 are hydrogen or lower alkyl, and,

- R^6 and R^7, and/or, R^3 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO_2 or N, and which may be substituted with,
  - $(CH_2)_n$-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N; or,

- when X_1 and X_2 both represent C-R^1, the 2 substituents R^1 may form together with the carbon atoms to which they are attached, a 5-membered heterocyclic ring comprising a nitrogen atom and optionally a second heteroatom selected from O, S or N;

b) X is O, S or NR^9, in which R^9 is selected from,

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

c) Y is selected from O, S or N-R^{12}, in which R^{12} is selected from:

- hydrogen, CN, OH, NH_2,
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with, cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO_2 or N, aryl, heteroaryl, OR^{10}, $COOR^{10}$ or $NR^{10}R^{11}$ in which R^{10} and R^{11} are the same or different and are selected from hydrogen or lower alkyl;

d) Z is chosen from CH-NO_2, O, S or NR^{13} in which R^{13} is selected from:

- hydrogen, CN, OH, NH_2, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$;

R^{14} and R^{15} being independently selected from hydrogen or lower alkyl, or, R^{14} and R^{15}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl, or,

- when Y is N-R^{12} and Z is N-R^{13}, R^{12} and R^{13} may form together a -CH=N- group or a -C=C- group,
- when X is N-R^9 and Z is N-R^{13}, R^9 and R^{13} may form together a -CH=N- group or a -C=C- group;

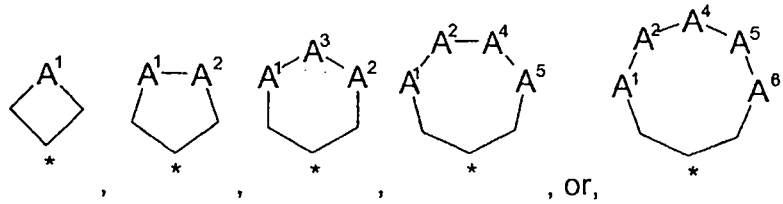
e) Z^1 is chosen from H, CH_3 or $NR^{16}R^{17}$ in which R^{16} and R^{17} are the same or different and are selected from:

- hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, $C(=O)R^{14}$, $C(=O)NR^{14}R^{15}$, OR^{14}, or,
- lower alkyl unsubstituted or substituted with one or several groups selected from OR^{14}, $COOR^{14}$ or $NR^{14}R^{15}$,

R^{14} and R^{15} being chosen from hydrogen or lower alkyl, and,

R^{14} and R^{15}, and/or, R^{16} and R^{17}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S or N, and which may be substituted with a lower alkyl;

f) A is a cycle chosen from:



, , , , or,

in which,

- A^1, A^2, A^3, A^4, A^5 and A^6 are the same or different and are selected from O, S, C, C(=O), SO, SO_2 or N-R^{18} in which R^{18} is selected from:

- hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N,
- lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO_2 or N, CN, $NR^{19}R^{20}$, $C(=O)NR^{19}R^{20}$, OR^{19}, $C(=O)R^{19}$ or $C(=O)OR^{19}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl;
- * represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;
- each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups, identical or different, selected from lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$, lower haloalkyl, CN, F, =O, $SO_2NR^{19}R^{20}$, OR^{19}, SR^{19}, $C(=O)OR^{19}$, $C(=O)NR^{19}R^{20}$ or $NR^{19}R^{20}$ in which R^{19} and R^{20} are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR^{21}, $NR^{21}R^{22}$, $COOR^{21}$ or $CONR^{21}R^{22}$ in which R^{21} and R^{22} are identical or different and are selected from hydrogen or lower alkyl, and,
  R^{19} and R^{20}, and/or, R^{21} and R^{22}, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- 2 atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N;

provided that not more than two of the groups A^1, A^2, A^3, A^4, A^5 and A^6 simultaneously represent a heteroatom;

of their tautomeric forms, their racemic forms or their isomers and of their pharmaceutically acceptable derivatives,

it being understood that,

lower alkyl and lower alkylene denote straight and branched carbon chains having from 1 to 6 carbon atoms;

lower alkenyl and lower alkenylene denote straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one double bond;
lower alkynyl and lower alkynylene denote straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one triple bond;
lower haloalkyl includes a lower alkyl as defined above, substituted with one or several halogens;
aryl refer to an aromatic carbocycle containing between 6 and 10 carbon atoms;
heteroaryl denote an aromatic cycle which have from 5 to 10 ring atoms, from 1 to 4 of which are independently selected from the group consisting of O, S, and N;
heterocyclic ring include heteroaryl as defined above and cycloalkyl or cycloalkenyl interrupted with 1, 2 or 3 heteroatoms chosen from O, S, S(=O), SO_2, or N;
for the preparation od a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

27. Use according to claim 26 in which said compound is a compound of formula (I) in which X_1, X_2, X_3, X_4, X, Y, Z and A are as defined in claim 25.

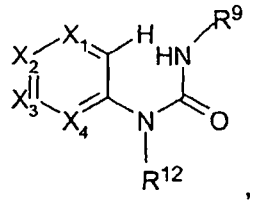
28. Use of a compound according to any one of claims 1 to 23 for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

29. Use according to any one of claims 26 to 28 in which said disorder is selected from T-cell-related diseases, autoimmune diseases, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease, asthma, cancer, acquired immune deficiency syndrome, allergy or inflammatory bowel disease.

30. A method for the prevention or the treatment of a disorder for which a therapy by a PDE7 inhibitor is relevant , comprising administering to a mammal in need thereof, an effective amount of a compound according to any one of claims 1 to 23.

31. A method according to claim 30 in which said disorder is selected from T-cell-related diseases, autoimmune diseases, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease, asthma, cancer, acquired immune deficiency syndrome, allergy or inflammatory bowel disease.

32. A method for preparing a compound of formula (I) according to claim 1 in which Y is N-R^{12}, X is N-R^9 and Z is O comprising reacting a substituted urea of formula



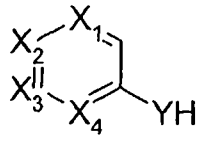
in which X_1, X_2, X_3, X_4, R_9 and R_{12} are as defined claim 1, with a cyclic ketone of formula



in which A is as defined in claim 1, to obtain said compound of formula (I) and isolating said compound of formula (I).

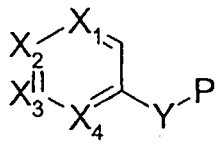
33. A method for preparing a compound of formula (I) according to claim 1 in which X_1, X_2, X_3, X_4, A and R^9 are as defined in claim 1 and Y is O, S or NH, said method comprising,

(1) reacting a compound (2a)



(2a)

in which X_1, X_2, X_3, X_4 are as defined in claim 1 and Y is O, S or NH, with a group P-LG in which P is a protecting group and LG is a leaving group to obtain compound (2b)

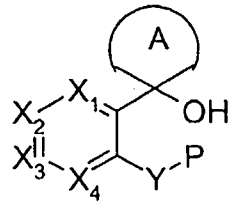


(2b)

(2) reacting compound (2b) with R-Li in which R is lower alkyl and then with a ketone of formula

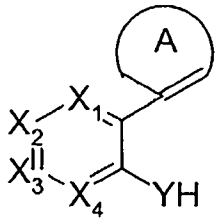


in which A is as defined in claim 1 to obtain compound (2c)



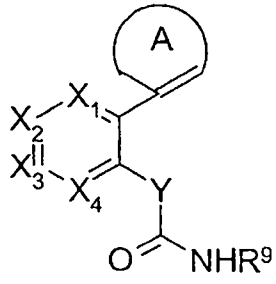
(2c)

(3) removing the protecting group P either under reductive conditions, acidic condition or basic condition to obtain compound (2d)



(2d)

(4) reacting compound (2d) with a group $O=C=N-R^9$ in which R^9 is as defined in claim 1 to obtain compound (2e)



(2e)

(5) reacting compound (2e) with an acid to obtain said compound of formula (I),

(6) isolating said compound of formula (I).

INTERNATIONAL SEARCH REPORT

Inte il Application No
PCT/EP 02/03594

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/70 C07D401/04 C07D403/04 A61K31/527 A61P29/00
C07D405/12 C07D413/12 C07D401/12

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, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 14686 A (ASTRA) 24 April 1997 (1997-04-24) claims; examples 25,26	1,24-29
A	WO 00 66560 A (AMERICAN HOME PRODUCTS) 9 November 2000 (2000-11-09) cited in the application claims	1,24-29

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[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
19 July 2002	19/08/2002

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	Francois, J

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

INTERNATIONAL SEARCH REPORT

Inten ial Application No
PCT/EP 02/03594

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TADASHI SASAKI ET AL.: "BRIDGEHEAD SUBSTITUTION REACTIONS OF 3-METHOXY-4-AZAHOMOADAMANTANE VIA N-ACYLIMINIUM IONS." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., vol. 8, 1984, pages 1863-8, XP002206882 CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 1472-7781 page 1865 -page 1867; figure 29	1

INTERNATIONAL SEARCH REPORT

ıtional application No.
PCT/EP 02/03594

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 30,31 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

Inter al Application No
PCT/EP 02/03594

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9714686 A	24-04-1997	AU 704133 B2	15-04-1999
		AU 7224396 A	07-05-1997
		BR 9610988 A	06-04-1999
		CZ 9801193 A3	16-09-1998
		EE 9800116 A	15-10-1998
		EP 0858451 A1	19-08-1998
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		AU 4814000 A	17-11-2000
		EP 1175404 A1	30-01-2002

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X MODELO DE UTILIDAD	( )	(X)
Indicación de que se solicita la concesión de una patente. ✓	( )	(X)
Datos de identificación del solicitante o de la persona que se presenta la solicitud. ✓	( )	(X)
Descripción de la Invención. ✓	( )	(X)
Dibujos de ser estos pertinentes.	( )	(X)
Comprobante de Pago de las tasas establecidas. ✓		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
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 ( )		
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	( )	( )

Edwar Novoa

Firma Responsable:

10-09-2003

Fecha: