



CARLOS TAMAYO & ASOCIADOS
INTERNATIONAL PATENT AND TRADEMARK OFFICE

Trademark	Marcas
Patent	Patentes
Permit Health	Registros Sanitarios
Software	Soporte Lógico
Commercial Name	Nombres Comerciales
Design	Diseños

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COM
DIVISION DE NUEVAS CREACIONES
E S D

SUPERINDUSTRIA Y COMERCIO
Radicación 03069643 00000001 Folios 27
Fecha (FOL): 2003-09-12 14:53:35
Traste 011 PCT-PATENT 379 FASE NACI 329 DEPLERE
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REF EXPEDIENTE 03-089643
PATENTE DE INVENCION PCT "QUINAZOLINAS COMO INHIBIDORAS
DE MMP-13"

Estimados señores

Damos alcance a la solicitud de patente PCT fase nacional presentada ante su Despacho y radicada el día 13 de Agosto del año en curso segun expediente citado en la referencia, con el fin de presentar copias de los siguientes documentos expedidos según el Tratado en Materia de Cooperación de Patentes

- 1 Copia del formulario de solicitud internacional, con su traducción al español
- 2 Copia del formulario de notificación de recepción de copia para registro de la solicitud internacional PCT/EP02/01979, con su traducción
- 3 Copia del formulario de notificación relativa a la presentación o transmisión del documento de prioridad con su traducción al español
- 4 Copia del formulario de notificación por la que se informa al solicitante sobre la comunicación de la solicitud internacional a las oficinas designadas, con su traducción al español
- 5 Copia del formulario de información sobre las oficinas elegidas notificadas sobre su elección, con su traducción al español
- 6 Copia del formulario de notificación de la transmisión del informe de búsqueda internacional o la declaración, con su traducción al español
- 7 Copia del formulario de notificación de la opinión escrita desde la autoridad examinadora preliminar internacional, con su traducción al español
- 8 Copia del formulario de notificación de la transmisión del informe de examen preliminar internacional, con su traducción
- 9 Copia del formulario de notificación de la inscripción de un cambio, con su traducción
- 10 Copia de la publicación internacional No WO 02/064572 A1 de la patente PCT/EP02/01979, con su

Carrera 7ª No 17 - 51 Of 710 Tels (571) 341 9841
(571) 400 9180 (571) 286 8037 • Celular (315) 317 1181
E-mail trademarks1@tutopia.com • Bogotá, Colombia, S.A
trademarks1@hotmail.com



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486 455

En consecuencia, ruego a usted tener en cuenta los anteriores documentos y una vez finiquitado esta diligencia, ordenar lo pertinente para que el expediente siga su curso normal

Del señor Jefe,

CARLOS ORLANDO MAYA RODRIGUEZ
No 17 117 818 expedida en Bogotá,
T P No 17 402 del C S J

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only

PCT/EP0-2 / 01979

International Application No.

11 FEB 2002

International Filing Date

(11 J2 2002)

EUROPEAN PATENT OFFICE

PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 018319 (A476) CD

Box No. I TITLE OF INVENTION	
QUINAZOLINES AS MMP-13 INHIBITORS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
WARNER-LAMBERT COMPANY	
201 Tabor Road Morris Plains, NJ 07950 UNITED STATES OF AMERICA	
State (that is, country) of nationality US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
ANDRIANJARA Charles 3 rue Auguste Dax 94260 FRESNES FRANCE	
State (that is, country) of nationality FR	State (that is, country) of residence: FR
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE, OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country.)	
HIRSCH Denise PFIZER Global Research and Development Fresnes Laboratoires, 3-9 rue de la Loge, B P 100 94265 FRESNES CEDEX FRANCE	
Telephone No. 33 1 40 96 32 00	Facsimile No. 33 1 40 96 76 90
Teleprinter No.	Agent's registration No. with the Office
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CHANTEL-BARVIAN Nicole
1225 Olivia Avenue
ANN ARBOR, MICHIGAN 48104
UNITED STATES OF AMERICA

This person is

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No with the Office

State (that is, country) of nationality

US

State (that is, country) of residence

US

This person is applicant for the purposes of

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

GAUDILLIERE Bernard
28 rue de Zilina
92000 NANTERRE
FRANCE

This person is

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No with the Office

State (that is, country) of nationality

FR

State (that is, country) of residence

FR

This person is applicant for the purposes of

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JACOBELLI Henry
65 avenue du Général de Gaulle
91550 PARAY VIEILLE POSTE
FRANCE

This person is

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No with the Office

State (that is, country) of nationality

FR

State (that is, country) of residence

FR

This person is applicant for the purposes of

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ORTWINE Daniel Fred
3594 Oak Park Drive
SALINE, MICHIGAN 48176
UNITED STATES OF AMERICA

This person is

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No with the Office

State (that is, country) of nationality

State (that is, country) of residence

This person is applicant for the purposes of

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

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

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Name and address. (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PATT William Chester
160 East summit
CHELSEA, MICHIGAN 48118
USA

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address. (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PHAM Ly
1609 Buchanana SW
GRAND RAPIDS, MICHIGAN 49507
USA

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address. (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KOSTLAN Catherine Rose
9876 Moon Road
SALINE, MICHIGAN 48176
USA

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address. (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WILSON Michael william
3520 Charter Place
ANN ARBOR, MICHIGAN 48105
USA

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

This person is applicant for the purposes of

☐ all designated States

☐ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below, at least one must be marked.

The following designations are hereby made under Rule 4.9(a)

Regional Patent

- ☒ AP ARIPO Patent GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☒ DE Germany | ☒ MA Morocco | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MG Madagascar | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MK The former Yugoslav Republic of Macedonia | |
| ☒ EE Estonia | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ ES Spain | ☒ MW Malawi | ☒ VN Viet Nam |
| ☒ FI Finland | ☒ MX Mexico | ☒ YU Yugoslavia |
| ☒ GB United Kingdom | ☒ MZ Mozambique | ☒ ZA South Africa |
| ☒ GD Grenada | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GE Georgia | | ☒ ZW Zimbabwe |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐	☐	☐
☐	☐	☐

Precautionary Designation Statement In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

- I** *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information. In such case, write "Continuation of Box No. ..." (Indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular*
- (i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available. In such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below*
- (ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked. In such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant*
- (iii) *If in Box No. II or in any of the sub-boxes of Box No. III the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America. In such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor*
- (iv) *If, in addition to the agent(s) indicated in Box No. IV there are further agents. In such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV*
- (v) *If, in Box No. V the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if in Box No. V the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part" In such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI) the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application,*
- (vi) *If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI*
- 2** *If with regard to the precautionary designation statement contained in Box No. V the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

Continuation of Box IV

DUFRESNE Guillaume
LAURENT Claire

Pfizer
Global Research and Development
Fresnes Laboratoires 3-9 rue de la Loge, B P 100
94285 FRESNES CEDEX
FRANCE

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application country	regional application * regional Office	international application receiving Office
item (1) 14 February 2001 (14/02/2001)	60/288 661	USA		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(II)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used)

ISA / EP

Request to use results of earlier search, reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority).

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)

Number of declarations

☐ Box No. VIII (i) Declaration as to the identity of the inventor☒ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent

1

☒ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application

1

☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America)☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty

Box No. VIII (ii) DECLARATION ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212 see Notes to Boxes Nos VIII VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4 17(ii) and 51bis 1(a)(ii)), in a case where the declaration under Rule 4 17(iv) is not appropriate

In relation to the international application No PCT/EP02/01979

WARNER-LAMBERT COMPANY is entitled to apply for and be granted a patent by virtue of the following

WARNER-LAMBERT COMPANY is entitled as employer of the inventors

ANDRIANJARA Charles, 3 rue August Daix, F - 94260 FRESNES, FRANCE
 CHANTEL BARVIAN Nicole, 1225 Olivia Avenue, ANN ARBOR, MICHIGAN 48104, USA
 GAUDILLIERE Bernard, 28 rue de Zilina, F - 92000 NANTERRE, FRANCE
 JACOBELLI Henry, 65 avenue du Général de Gaulle, F - 91550 PARAY VIEILLE
 POSTE, FRANCE
 ORTWINE Daniel Fred, 3594 Oak Park Drive, SALINE, MICHIGAN 48176, USA
 PATT William Chester, 160 East Summit, CHELSEA, MICHIGAN 48118, USA
 PHAM Ly, 1609 Buchanan SW, GRAND RAPIDS, MICHIGAN 49507, USA
 KOSTLAN Catherine Rose, 9876 Moon Road, SALINE, MICHIGAN 48176, USA
 WILSON Michael William, 3520 Charter Place, ANN ARBOR MICHIGAN 48105, USA

This declaration is made for the purposes of all designations, except the designation of the United States of America

☐ This declaration is continued on the following sheet, "Continuation of Box No VIII (ii)"

Box No. VIII (II) DECLARATION ENTITLEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213 see Notes to Boxes Nos. VIII VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (II) If this Box is not used, this sheet should not be included in the request

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4 17(III) and 51bis 1(a)(III))

In relation to this international application No PCT/EP02/01979

WARNER-LAMBERT COMPANY is entitled to claim priority of earlier application No US 60/268,661 by virtue of the following

WARNER-LAMBERT COMPANY is entitled as employer of the inventors,

- ANDRIANJARA Charles, 3 rue August Dax, F - 94260 FRESNES, FRANCE
- CHANTEL BARVIAN Nicole, 1225 Olivia Avenue, ANN ARBOR, MICHIGAN 48104, USA
- GAUDILLIERE Bernard, 28 rue de Zilina, F - 92000 NANTERRE, FRANCE
- JACOBELLI Henry, 65 avenue du Général de Gaulle, F - 91550 PARAY VIEILLE POSTE, FRANCE
- ORTWINE Daniel Fred, 3594 Oak Park Drive, SALINE, MICHIGAN 48176, USA
- PATT William Chester, 160 East Summit, CHELSEA, MICHIGAN 48118, USA

This declaration is made for the purposes of all designations

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (II)"

Box No. VIII (iv) DECLARATION INVENTORSHIP (only for the purposes of the designation of the United States of America)
The declaration must conform to the following standardized wording provided for in Section 214 see Notes to Boxes Nos. VII, VIII (i) to (iv) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request

**Declaration of inventorship (Rules 4.17(iv) and 51bx.1(a)(iv))
for the purposes of the designation of the United States of America.**

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/ (if furnishing declaration pursuant to Rule 26ter)

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10 any claim to foreign priority and I have identified below under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: 60/268,661, US, 14 February 2001

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

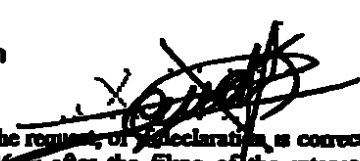
Name. **ANDRIANJARA Charles**

Residence. **FRESNES FRANCE**

(city and either US state, if applicable, or country)

Mailing Address. **3 rue August Doh, F - 84260 FRESNES FRANCE**

Citizenship: **French**

Inventor's Signature: 

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: **03/04/02**

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: **CHANTEL BARVIAN Nicole**

Residence **ANN ARBOR, MICHIGAN 48104, USA**

(city and either US state, if applicable, or country)

Mailing Address. **1225 Olivia Avenue ANN ARBOR, MICHIGAN 48104 USA**

Citizenship: **US**

Inventor's Signature: 

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: **2 4/2/02**

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)"

Continuation of Box No. VIII (i) to (v) **DECLARATION**

If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII ..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name. GAUDILLIERE Bernard

Residence NANTERRE, FRANCE

Mail address 28 rue de Zilina, F - 92000 NANTERRE, FRANCE

Citizenship French

Inventor's signature

Date

04/08/02

Name JACOBELLI Henry

Residence. PARAY VIEILLE POSTE, FRANCE

Mail address 65 avenue du Général de Gaulle, F - 91550 PARAY VIEILLE POSTE, FRANCE

Citizenship French

Inventor's signature

Date

03.04.02

Name ORTWINE Daniel Fred

Residence SALINE, MICHIGAN 48176, USA

Mail address 3594 Oak Park Drive, SALINE, MICHIGAN 48176 USA

Citizenship US

Inventor's signature

Date

3/27/02

Name PATT William Chester

Residence: CHELSEA, MICHIGAN 48118, USA

Mail address 160 East Summit, CHELSEA, MICHIGAN 48118, USA

Citizenship US

Inventor's signature

Date

3/27/02

Name PHAM Ly

Residence GRAND RAPIDS, MICHIGAN 49507, USA

Mail address 1609 Buchanan SW, GRAND RAPIDS, MICHIGAN 49507, USA

Citizenship US

Inventor's signature

Date

03/02/02

Continuation of Box No. VIII (i) to (v) DECLARATION

If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII ..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name KOSTLAN Cathenne rose

Résidence. SALINE, MICHIGAN 48176, USA

Mailing Address. 9876 Moon Road, SALINE, MICHIGAN 48176, USA

Inventor's Signature

Cathenne Rose Kostlan

Date

03/12/02

Name WILSON Michael William

Résidence ANN ARBOR, MICHIGAN 48105

Mailing Address. 3520 Charter Place, ANN ARBOR, MICHIGAN 48105

Inventor's Signature

Michael William Wilson

Date

03/12/02

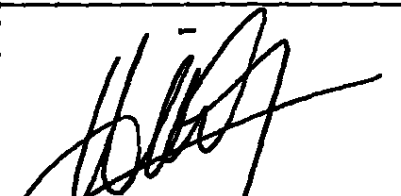
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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item)	Number of items
(a) the following number of sheets in paper form	1 ☒ fee calculation sheet	
request (including declaration sheets)	2 ☐ original separate power of attorney	
description (excluding sequence listing part)	3 ☐ original general power of attorney	
claims	4 ☐ copy of general power of attorney, reference number, if any	
abstract	5 ☐ statement explaining lack of signature	
drawings	6 ☒ priority document(s) identified in Box No. VI as item(s).	
Sub-total number of sheets	7 ☐ translation of international application into (language)	
sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form, see (b) below)	8 ☐ separate indications concerning deposited microorganism or other biological material	
Total number of sheets	9 ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(b) sequence listing part of description filed in computer readable form	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	
(i) ☐ only (under Section 801(a)(i))	(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii) in right column)	10 ☐ other (specify)	
Figure of the drawings which should accompany the abstract.	Language of filing of the international application. ENGLISH	

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

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



KIRSCH Denise
Professional Representative
before the European Patent Office

For receiving Office use only		2. Drawings: ☐ received. ☐ not received.
1 Date of actual receipt of the purported international application.	11 FEB. 2002 (11-02-2002)	
3 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application.		
4 Date of timely receipt of the required corrections under PCT Article 11(2):		
5 International Searching Authority (if two or more are competent): ISA /	6 ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau.

~~SA~~
4/60**PCT****SOLICITUD**

Los abajo firmantes solicitan que se procese la presente solicitud internacional de acuerdo con el Tratado de Cooperación de Patentes

Para uso exclusivo de la Oficina Receptora

No de Solicitud Internacional **PCT/EP02/01979**

Fecha de presentación internacional 11 de febrero de 2002
(11 02 2002)

Nombre de la Oficina Receptora y "Solicitud Internacional de PCT", OFICINA EUROPEA DE PATENTES, SOLICITUD INTERNACIONAL DE PCT

Referencia de archivo del solicitante o agente (si se desea) (máximo 12 caracteres) 018319 (A476)CD

Casillero No I - TÍTULO DE LA INVENCION

"QUINAZOLINAS COMO INHIBIDORAS DE MMP-13"

Casillero No II - SOLICITANTE

[] Esta persona es también inventor

470
169

Nombre y domicilio (Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

WARNER-LAMBERT COMPANY

201 Tabor Road, Morris Plains, NJ 07950, Estados Unidos de Norteamérica

Teléfono No (en blanco)

Fax No (en blanco)

Teleprinter No (en blanco)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☒ todos los estados designados excepto Estados Unidos de Norteamérica

☐ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Casillero No III - OTROS SOLICITANTES Y/O INVENTORES

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personeria jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

ANDRIANJARA Charles, 3 rue Auguste Daix, 94260 Fresnes, Francia

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente *(si se marca este casillero, no completar lo que sigue)*

No de registro del solicitante con la oficina ---

Estado(es decir, país) de nacionalidad FR

Estado(es decir, país) de residencia FR

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

471

☐ los estados indicados en el casillero suplementario

☒ Los otros solicitantes y/o inventores se indican en una hoja a continuación

Casillero No IV - AGENTE O REPRESENTANTE COMUN, O DOMICILIO PARA CORRESPONDENCIA

La persona identificada más abajo es/ha sido designada por la presente para actuar en nombre del solicitante ante las Autoridades Internacionales competentes como

☒ Agente, ☐ Representante Común

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personeria juridica, la designación oficial completa El domicilio debe incluir el código postal y el país)

HIRSCH Denise, PFIZER, Global Research and Development,
Fresnes Laboratories, 3-9 rue de la Loge, B P 100, 94265
Fresnes Cedex, Francia

Teléfono No 33 1 40 96 32 00

Fax No 33 1 40 96 76 90

Teleprinter No (en blanco)

No de registro del agente con la oficina (en blanco)

[] **Domicilio para correspondencia** Marcar este casillero cuando no se haya designado agente o representante común y el espacio anterior se utilice en cambio para indicar un domicilio especial al que se deba enviar la correspondencia

Formulario PCT/RO/101 (Primera página) (marzo de 2001, reimpreso en enero de 2002)

Ver notas al formulario de solicitud

PCT/EP02/0197

Página No 2

Continuación del Casillero No III - OTROS SOLICITANTES Y/O INVENTORES

Si no se usa ninguno de los casilleros siguientes, esta página no debería incluirse en la solicitud

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica mas abajo ningún Estado de residencia)

CHANTEL-BARVIAN Nicole, 1225 Olivia Avenue, Ann Arbor,
Michigan 48104, Estados Unidos de Norteamérica

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no
completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de
Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con
personería jurídica, la designación oficial completa El
domicilio debe incluir el código postal y el país El país
del domicilio que se indica en este Casillero es el Estado

del Solicitante (es decir, país) de residencia si no se indica mas abajo ningún Estado de residencia)

GAUDILLIERE Bernard, 28 rue de Zilina, 92000 Nanterre, Francia

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad FR

Estado (es decir, país) de residencia FR

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país

del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

JACOBELLI Henry, 65 avenue du Général de Gaulle, 91550 Paray Vieille Poste, Francia

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad FR

Estado (es decir, país) de residencia FR

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El

476

domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

ORTWINE Daniel Fred, 3594 Oak Park Drive, Saline, Michigan
48176, Estados Unidos de Norteamérica

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad (en blanco)

Estado (es decir, país) de residencia (en blanco)

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

☒ Los otros solicitantes y/o inventores se indican en una hoja a continuación

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Formulario PCT/RO/101 (página de continuación) (marzo de 2001, reimpreso en enero de 2002)

Ver notas al formulario de solicitud

PCT/EP02/0197

Página No 3

Continuación del Casillero No III - OTROS SOLICITANTES Y/O INVENTORES

Si no se usa ninguno de los casilleros siguientes, esta página no debería incluirse en la solicitud

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

PATT William Chester, 160 East summit, Chelsea, Michigan 48118, Estados Unidos de Norteamérica

Esta persona es

[] solicitante solamente,

478

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica mas abajo ningún Estado de residencia)

PHAM Ly, 1609 Buchanan SW, Grand Rapids, Michigan 49507,

Estados Unidos de Norteamérica

Esta persona es

478
479

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

KOSTLAN Catherine Rose, 9876 Moon Road, Saline, Michigan
48176, Estados Unidos de Norteamérica

480

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☒ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

Nombre y Domicilio

(Apellido seguido del nombre, para las entidades con personería jurídica, la designación oficial completa El domicilio debe incluir el código postal y el país El país del domicilio que se indica en este Casillero es el Estado del Solicitante (es decir, país) de residencia si no se indica más abajo ningún Estado de residencia)

WILSON Michael William, 3520 Charter Place, Ann Arbor,
Michigan 48105, Estados Unidos de Norteamérica

Esta persona es

☐ solicitante solamente,

☒ solicitante e inventor,

☐ inventor solamente (si se marca este casillero, no completar lo que sigue)

No de registro del solicitante con la oficina ---

Estado (es decir, país) de nacionalidad US

Estado (es decir, país) de residencia US

Esta persona es solicitante para los fines de

☐ todos los estados designados

☐ todos los estados designados excepto Estados Unidos de Norteamérica

☐ solamente los Estados Unidos de Norteamérica

☐ los estados indicados en el casillero suplementario

☐ Los otros solicitantes y/o inventores se indican en una hoja a continuación

Formulario PCT/RO/101 (página de continuación) (marzo de 2001, reimpreso en enero de 2002)

Ver notas al formulario de solicitud

PCT/EP02/0197

Página No 4

Casillero No V - DESIGNACIÓN DE ESTADOS

Marcar los casilleros correspondientes, por lo menos se debe marcar uno

Las siguientes designaciones se realizan conforme a la norma 4 9(a)

Patente Regional

(X) AP Patente ARIPO GH Ghana, GM Gambia, KE Kenia, LS Lesoto, MW Malawi, MZ Mozambique, SD Sudán, SL Sierra Leona, SZ Suazilandia, TZ República Unida de Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe y cualquier otro Estado que sea Estado contratante del Protocolo de Harare y de PCT (si se desea otro tipo de protección o tratamiento, especificarlo en la línea de puntos)---

(X) EA Patente Euroasiática AM Armenia, AZ Azerbaijan, BY Belarus, KG Kirgistan, KZ Kazakstan, MD República de Moldovia, RU Federación Rusa, TJ Tajikistan, TM Turkmenistan, y cualquier otro Estado que sea Estado contratante de la Convención de Patentes Euroasiática y del PCT

(X) EP Patente Europea AT Austria, BE Bélgica, CH y LI Suiza y Liechtenstein, CY Chipre, DE Alemania, DK Dinamarca, ES España, FI Finlandia, FR Francia, GB Reino Unido, GR Grecia, IE Irlanda, IT Italia, LU Luxemburgo, MC

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Mónaco, NL Holanda, PT Portugal, SE Suecia, TR Turquía y cualquier otro Estado que sea un Estado contratante de la Convención de Patentes Europea y de PCT

(X) OA Patente OAPI BF Burkina Faso, BJ Benin, CF República Centro Africana, CG Congo, CI Costa de Marfil, CM Camerún, GA Gabonia, GN Guinea, GQ Guinea Ecuatorial, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Nigeria, SN Senegal, TD El Chad, TG Togo, y cualquier otro Estado que sea miembro de OAPI y un Estado contratante de PCT (Si se desea algun otro tipo de proteccion o tratamiento, especificarlo en la línea de puntos)---

Patente Nacional (Si se desea algún otro tipo de proteccion o tratamiento, especificar en la linea de puntos)

(X) AE Emiratos Árabes Unidos	(X) LC Santa Lucia
(X) AG Antigua y Barbuda	(X) LK Sri Lanka
(X) AL Albania	(X) LR Liberia
(X) AM Armenia	(x) LS Lesoto
(X) AT Austria	(X) LT Lituania
	(X) LU Luxemburgo
(X) AZ Azerbaiján	(X) LV Latvia
(X) BA Bosnia y Herzegovina	(X) MA Marruecos
(X) BB Barbados	(X) MD República de Moldovia
(X) BG Bulgaria	(X) MG Madagascar

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(X) BR Brasil	(X) MK Antigua República Yugoslava de Macedonia
(X) BY Belarus	(X) MN Mongolia
(X) BZ Belize	(X) MW Malawi
(X) CA Canadá	(X) MX Méjico
(X) CH y LI Suiza y Liechtenstein	(X) MZ Mozambique
(X) CN China	(X) NO Noruega
(X) Colombia	(X) NZ Nueva Zelanda
(X) Costa Rica	(X) OM Omán
(X) CU Cuba	(X) PH Filipinas
	(X) PL Polonia
(X) CZ República Checa	(X) PT Portugal
(X) DE Alemania	(X) RO Rumania
(X) DK Dinamarca	(X) RU Federación Rusa
(X) DM Dominica	(X) SD Sudán
(X) DZ Algeria	(X) SE Suecia
(X) EE Estonia	(X) SG Singapur
(X) ES España	(X) SI Eslovenia
(X) FI Finlandia	(X) SK Eslovaquia
(X) GB Reino Unido	(X) SL Sierra Leona
(X) GD Granada	(X) TJ Tajikistan
(X) GE Georgia	(X) TM Turkmenistan
	(X) TN Tunisia
(X) GH Ghana	(X) TR Turquía

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(X) GM Gambia	(X) TT Trinidad y Tobago
(X) HR Croacia	(X) TZ República Unida de Tanzania
(X) HU Hungría	(X) UA Ucrania
(X) ID Indonesia	(X) UG Uganda
(X) IL Israel	(X) US Estados Unidos de Norteamérica
(X) IN India	(X) UZ Uzbekistan
(X) IS Islandia	(X) VN Vietnam
(X) JP Japón	(X) YU Yugoslavia
(X) KE Kenia	(X) ZA Sudáfrica
(X) KG Kirgiztan	(X) ZM Zambia
	(X) ZW Zimbabwe
(X) KP República Democrática Popular de Corea	
(X) KR República de Corea	
(X) KZ Kazakhstan	

Casilleros reservados para designar Estados que se han convertido en miembro del PCT luego de la emisión de esta página

[]	[]	[]
[]	[]	[]

Declaración de Designación Precautoria Además de las designaciones realizadas anteriormente, el solicitante

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también realiza, según la norma 4 9(b), todas las designaciones que puedan permitirse según el PCT con excepción de la/s designación/es indicadas en el Casillero Suplementario por estar excluidas del alcance de esta declaración. El solicitante declara que aquellas designaciones adicionales están sujetas a confirmación y que cualquier designación que no sea confirmada antes de la caducidad de los 15 meses desde la fecha de prioridad se considerará como retirada por el solicitante al momento de la finalización de ese límite de tiempo (La confirmación (incluyendo los aranceles) debe llegar a la Oficina Receptora dentro del límite de tiempo de 15 meses)

Formulario PCT/RO/101 (segunda página) (enero de 2002),

Ver notas al formulario de solicitud

PCT/EP02/0197

Página No 5

Casillero Suplementario Si no se utiliza el casillero suplementario, no se necesita incluir esta página en la solicitud

1 Si en cualquiera de los casilleros, excepto los casilleros Nos VIII(1) a (v) para el cual se proporciona

un casillero de continuación especial, el espacio no fuera suficiente para incluir toda la información en tal caso escribir "Continuación del Casillero No " [indicar el número de casillero] y proporcionar la información de la misma forma que se requiere de acuerdo con los títulos del casillero en el cual el espacio no resulta suficiente, en especial

(1) si más de dos personas son solicitantes y/o inventores y no se encuentra disponible una "página continuación" en tal caso, escribir "Continuación del Casillero No III" e indicar para cada persona adicional, el mismo tipo de información que se requiere en el Casillero No III El país del domicilio que se indica en el casillero es el Estado de residencia (es decir, país) del Solicitante si no se indica más abajo el estado de residencia,

(11) si, en el Casillero No II o en cualquiera de los subcasilleros del casillero No III, se marca la opción "los estados indicados en el Casillero Suplementario" en tal caso, escribir "Continuación del Casillero No II" o "Continuación del Casillero No III" o "Continuación de los Casilleros No II y No III" (según sea el caso), indicar el nombre del/os Solicitante/s y, junto a cada nombre, el Estado (y/o, cuando corresponda, patente ARIPO,

Euroasiática, Europea u OAPI) para los fines para los que la persona mencionada es solicitante,

(iii) si, en el Casillero No II o en cualquiera de los subcasilleros del casillero No III, el inventor o el inventor/solicitante no fuera inventor para los fines de todos los estados designados o para los fines de los Estados Unidos de Norteamérica en tal caso, escribir "Continuación del Casillero No II" o "Continuación del Casillero No III" o "Continuación de los Casilleros No II Y No III" (según sea el caso), indicar el nombre del/os inventor/es y, junto a cada nombre, el Estado (y/o, cuando corresponda, patente ARIPO, Euroasiática, Europea u OAPI) para los fines para los que la persona mencionada es inventor,

(iv) si, además de los agentes indicados en el Casillero No IV, existen otros agentes en tal caso, escribir "Continuación del Casillero No IV" e indicar para cada agente adicional el mismo tipo de información que se requiere en el Casillero No IV,

(v) si, en el Casillero No V, el nombre de cualquier estado (u OAPI) aparece con la indicación "patente de adición", o "certificado de adición", o si, en el Casillero

~~498~~
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No V el nombre de los Estados Unidos de Norteamérica aparece con la indicación "Continuación" o "Continuación en parte" en tal caso, escribir "Continuación del Casillero No V" y el nombre de cada estado involucrado (u OAPI), y luego del nombre de cada estado (u OAPI), el número de título relacionado o solicitud relacionada y la fecha de concesión del título relacionado o de presentación de la solicitud relacionada,

(vi) si, en el Casillero No VI hay más de tres solicitudes anteriores de las cuales se reivindica prioridad en tal caso, escribir "Continuación del Casillero No VI" e indicar para cada solicitud anterior adicional, el mismo tipo de información que se requiere en el Casillero No VI,

2 Si con respecto a la declaración de designación precautoria contenida en el Casillero No V, el solicitante desea excluir a un estado del alcance de dicha declaración en tal caso, escribir "Designacion excluida de la declaración de designación precautoria" e indicar el nombre o el código de dos letras de cada estado excluido

Continuación del Casillero No IV

DUFRESNE Guillaume

LAURENT Claire

490

Pfizer, Global Research and Development, Fresnes
Laboratories, 3-9 rue de la Loge, B P 100, 94265 Fresnes
Cedex, Francia

Formulario PCT/RO/101 (página suplementaria) (marzo de 2001,
reimpreso en enero de 2002)

Ver notas al formulario de solicitud

PCT/EP02/0197

Página No 6

Casillero No VI REIVINDICACION DE PRIORIDAD

Se reivindica por la presente la prioridad de la siguiente
solicitud anterior

		Cuando la solicitud anterior sea		
Fecha de Presentación de sol anterior (dia/mes/año)	No de Solicitud Anterior	Sol nacional pais	Sol regional * Oficina regional	Sol Internacio- nal Oficina receptora
Ítem (1) 14 de febrero de 2001 (14/02/2001)	60/268661	EE UU		
Ítem (2)				
Ítem (3)				

ítem (4)				
ítem (5)				

[] Otras reivindicaciones de prioridad se indican en le Casillero Suplementario

Por la presente se solicita a la Oficina Receptora que prepare y transmita a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) (sólo si la solicitud anterior fue presentada en la Oficina que para los fines de la presente solicitud internacional es la Oficina Receptora) identificada más arriba como

[] todos los ítems, [] ítem (1), [] ítem (2), [] ítem (3), [] ítem (4), [] ítem (5), [] otro, ver el casillero suplementario

* En el caso en que la solicitud anterior sea una solicitud de ARIPO, indicar por lo menos un país miembro de la Convención de París para la Protección de la Propiedad Industrial o uno que sea miembro de la Organización Mundial de Comercio para el cual se presentó dicha solicitud anterior (Norma 4 10(b)(11)) ---

Elección de la Autoridad de Búsqueda Internacional ("ISA")

(Si dos o mas Autoridades de Busqueda Internacional resultan competentes para llevar a cabo la búsqueda internacional, indicar la Autoridad elegida, se puede utilizar el código de dos letras) ISA/EP

Solicitud para usar los resultados de una busqueda anterior, referencia a tal búsqueda

(Si la Autoridad de Busqueda Internacional hubiera llevado a cabo o hubiera solicitado una busqueda anterior)

Fecha (día, mes, año) ---

Número ---

País (u Oficina Regional) ---

Casillero No VIII DECLARACIONES

Las siguientes declaraciones se encuentran contenidas en los casilleros Nos VIII(1) a (v) (marcar los casilleros que correspondan de los que aparecen más abajo e indicar en la columna de la derecha la cantidad de cada tipo de declaración)

[] Casillero No VIII(1) Declaración sobre la identidad del inventor (Número de declaraciones) ---

☒ Casillero No VIII(ii) Declaración sobre los derechos del solicitante, en la fecha de presentación internacional, para solicitar y obtener la concesión de una patente (Número de declaraciones) 1

☒ Casillero No VIII(iii) Declaración sobre los derechos del solicitante, en la fecha de presentación internacional, para reivindicar la prioridad de una solicitud anterior (Número de declaraciones) 1

☐ Casillero No VIII(iv) Declaración sobre inventores (sólo para los fines de la designación en los Estados Unidos de Norteamérica (Numero de declaraciones) ---

☐ Casillero No VIII(v) Declaración sobre revelaciones no perjudiciales o excepciones por falta de novedad (Numero de declaraciones) ---

Formulario PCT/RO/101 (tercera página) (marzo de 2001, reimpreso en enero de 2002)

Ver notas al formulario de solicitud

Página No 5

Casillero No VIII (ii) DERECHO PARA SOLICITAR Y OBTENER UNA PATENTE

49A

La declaración debe conformarse al texto estandarizado provisto en el Artículo 212, véanse las Notas sobre los Casilleros Nos VIII, VIII (1) al (v) (en general) y las Notas específicas sobre los Casilleros VIII (11) Si no se utiliza este casillero, no deberá incluirse esta página en la solicitud

Declaración sobre los derechos del solicitante con respecto a la fecha de presentación internacional para solicitar y obtener la concesión de una patente (Norma 4 17(11) y 51bis 1(a)(11)), cuando la declaración de la Norma 4 17(1v) no fuera apropiada

Con respecto a la solicitud internacional No PCT/EP02/01979, WARNER-LAMBERT COMPANY tiene derecho de solicitar y obtener la concesión de una patente en virtud de lo siguiente

WARNER-LAMBERT COMPANY tiene derechos como empleador de los inventores

ANDRIANJARA Charles, 3 rue August Daix, F-94260 Fresnes, Francia

CHANTEL BARVIAN Nicole, 1225 Olivia Avenue, Ann Arbor, Michigan 48104, Estados Unidos de Norteamérica

GAUDILLIERE Bernard, 28 rue de Zilina, F-92000 Nanterre, Francia

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JACOBELLI Henry, 65 avenue du Général de Gaulle, F-91550
Paray Vieille Poste, Francia

ORTWINE Daniel Fred, 3594 Oak Park Drive, Saline, Michigan
48176, Estados Unidos de Norteamérica

PATT William Chester, 160 East Summit, Chelsea, Michigan
48118, Estados Unidos de Norteamérica

PHAM Ly, 1609 Buchanan SW, Grand Rapids, Michigan 49507,
Estados Unidos de Norteamérica

KOSTLAN Catherine Rose, 9876 Moon Road, Saline, Michigan
48176, Estados Unidos de Norteamérica

WILSON Michael William, 3520 Charter Place, Ann Arbor,
Michigan 48105, Estados Unidos de Norteamérica

Esta declaración se realiza para los fines de todas las
designaciones, con excepción de la designación de los
Estados Unidos de Norteamérica

[] Esta declaración continúa en la siguiente página,
"Continuación del Casillero No VIII(11)"

Formulario PCT/RO/101 (página de declaración (11)) (marzo
de 2001, reimpreso en enero de 2002)

Ver Notas al formulario de solicitud

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Casillero No VIII (111) DERECHO DE REIVINDICAR PRIORIDAD

La declaración debe conformarse al texto estandarizado provisto en el Artículo 213, veanse las Notas sobre los Casilleros Nos VIII, VIII (1) al (v) (en general) y las Notas específicas sobre los Casilleros VIII (111) Si no se utiliza este casillero, esta página no deberá incluirse en la solicitud

Declaracion sobre los derechos del solicitante con respecto a la fecha de presentación internacional para reivindicar la prioridad de la solicitud anterior que se especifica más abajo, cuando el solicitante no sea el solicitante que presentó la solicitud anterior o cuando el nombre del solicitante haya cambiado desde la presentación de la solicitud anterior (Normas 4 17(111) y 51bis 1(a)(111))

Con respecto a la solicitud internacional No PCT/EP02/01979, WARNER-LAMBERT COMPANY tiene derecho de reivindicar prioridad de la solicitud estadounidense anterior No 60/268 661 en virtud de lo siguiente

WARNER-LAMBERT COMPANY tiene derechos como empleador de los inventores,

ANDRIANJARA Charles, 3 rue August Daix, F-94260 Fresnes, Francia

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CHANTEL BARVIAN Nicole, 1225 Olivia Avenue, Ann Arbor,
Michigan 48104, Estados Unidos de Norteamérica

GAUDILLIERE Bernard, 28 rue de Zilina, F-92000 Nanterre,
Francia

JACOBELLI Henry, 65 avenue du Général de Gaulle, F-91550
Paray Vieille Poste, Francia

ORTWINE Daniel Fred, 3594 Oak Park Drive, Saline, Michigan
48176, Estados Unidos de Norteamérica

PATT William Chester, 160 East Summit, Chelsea, Michigan
48118, Estados Unidos de Norteamérica

Esta declaración se realiza para los fines de todas las
designaciones

[] Esta declaración continúa en la siguiente página,
"Continuación del Casillero No VIII(111)"

Formulario PCT/RO/101 (página de declaración (111)) (marzo
de 2001, reimpreso en enero de 2002)

Ver Notas al formulario de solicitud

Página No 9

**Casillero No VIII (iv) DECLARACION INVENTORES (solamente
para los fines de la designación de los Estados Unidos de
Norteamérica)**

La declaración debe conformarse al texto estandarizado provisto en el Artículo 214, véanse las Notas sobre los Casilleros Nos VIII, VIII (i) al (v) (en general) y las Notas específicas sobre los Casilleros VIII (iv) Si no se utiliza este casillero, esta página no deberá incluirse en la solicitud

**Declaración de inventores (Norma 4 17(iv) y
5lbis 1(a) (iv)) para los fines de la designación de los
Estados Unidos de Norteamérica**

Por la presente declaro que creo ser el primer y unico inventor original (si a continuación aparece solo un nombre) o un inventor conjunto (si a continuación aparecen varios nombres) del objeto que se reivindica y para el cual se desea obtener una patente

Esta declaración está dirigida a la solicitud internacional de la que forma parte (si se presenta la declaración junto con la solicitud)

Esta declaración está dirigida a la solicitud internacional No PCT/[en blanco] (si se presenta la solicitud conforme a la Norma 26ter)

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Por la presente declaro que mi domicilio, domicilio postal y nacionalidad son los que se indican a continuación de mi nombre

Por la presente afirmo que he revisado y comprendo el contenido de la solicitud internacional identificada más arriba, incluyendo las reivindicaciones de dicha solicitud. En el pedido de dicha solicitud he identificado, en cumplimiento con la Norma PCT 4.10, cualquier reivindicación de prioridad extranjera, y he identificado más abajo, bajo el título "Solicitudes Anteriores", con número de solicitud, país o miembro de la Organización Mundial del Comercio, día, mes y año de presentación, cualquier solicitud para obtener una patente o certificado de inventor presentado en un país distinto de los Estados Unidos de Norteamérica, incluyendo cualquier solicitud internacional de PCT que designe al menos un país distinto de los Estados Unidos de Norteamérica, con una fecha de presentación anterior a la de la solicitud sobre la cual se reivindica prioridad extranjera.

Solicitudes Anteriores 60/268 661, EE UU , 14 de febrero de 2001

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Reconozco por la presente el deber de revelar la información que sea relevante para el patentamiento conforme al Título 37 del Código de Reglamentaciones Federales, Artículo 1 56, incluyendo las solicitudes de continuación en parte, información relevante que estuviera disponible entre la fecha de presentación de la solicitud anterior y la fecha de presentación internacional de PCT de la solicitud de continuación en parte

Declaro que todos los testimonios prestados en la presente son auténticos y que todos los testimonios prestados sobre la información son, a mi leal saber y entender, auténticos, y que dichos testimonios fueron prestados a sabiendas de que todo testimonio deliberadamente falso y declaración similar es pasible de sanción con multa o prisión, o ambas, conforme al Artículo 1001 del Título 18 del Código de los Estados Unidos de Norteamérica y que dichos falsos testimonios pueden poner en peligro la validez de la solicitud o de cualquier patente concedida por la misma

Nombre ANDRIANJARA, Charles

Domicilio (ciudad y el estado de EE UU , si corresponde, o país) Fresnes, Francia

501

Domicilio Postal 3 rue August Daix, F-94260 Fresnes,
Francia

Ciudadanía francesa

Firma del inventor (si no está contenida en el pedido o si la declaración se corrige o agrega bajo la Norma 26ter luego de la presentación de la solicitud internacional La firma debe ser la del inventor y no la del agente) [sigue una firma ilegible]

Fecha (de la firma que no está contenida en el pedido, o de la declaración que se corrige o agrega bajo la Norma 26ter luego de la presentación de la solicitud internacional) 04/03/02

Nombre CHANTEL BARVIAN Nicole

Domicilio (ciudad y el estado de EE UU , si corresponde, o país) Ann Arbor, Michigan 48104, EE UU

Domicilio Postal 1225 Olivia Avenue, Ann Arbor, Michigan 48104, EE UU

Ciudadanía estadounidense

Firma del inventor (si no esta contenida en el pedido o si la declaración se corrige o agrega bajo la Norma 26ter luego de la presentación de la solicitud internacional La firma debe ser la del inventor y no la del agente) [sigue una firma ilegible]

32

Fecha (de la firma que no está contenida en el pedido, o de la declaración que se corrige o agrega bajo la Norma 26ter luego de la presentación de la solicitud internacional) 2/4/02

[X] Esta declaración continúa en la página siguiente, "Continuación del Casillero No VIII (iv)"

Formulario PCT/RO/101 (página de declaración (iv)) (marzo de 2001, reimpreso en enero de 2002)

Ver Notas al formulario de solicitud

Página No 10

Casillero No VIII (i) a (v) DECLARACION

Si el espacio no es suficiente en cualquiera de los Casilleros VIII (i) al (v) para proporcionar toda la información, incluyendo el caso en que se deban nombrar más de dos inventores en el Casillero VIII (iv), en tal situación, escribir "Continuación del Casillero No VIII" (indicar el número de ítem del casillero) y proporcionar la información del mismo modo que se requiere para los fines del Casillero en el cual el espacio resultó insuficiente. Si es necesario más espacio con respecto a dos o más declaraciones, se deberá usar un casillero de

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continuación separado para cada una de tales
declaraciones Si no se utiliza este casillero, esta
página no deberá incluirse en la solicitud

Nombre GAUDILLIERE Bernard

Domicilio Nanterre, Francia

Domicilio Postal 28 rue de Zilina, F-92000 Nanterre,
Francia

Ciudadanía francesa

Firma del inventor [sigue una firma ilegible]

Fecha 08/04/02

Nombre JACOBELLI Henry

Domicilio Paray Vieille Poste, Francia

Domicilio Postal 65 avenue du General de Gaulle, F-91550

Paray Vieille Poste, Francia

Ciudadanía francesa

Firma del inventor [sigue una firma ilegible]

Fecha 04/03/02

Nombre ORTWINE Daniel Fred

Domicilio Saline, Michigan 48176, EE UU

Domicilio Postal 3594 Oak Park Drive, Saline, Michigan
48176, EE UU

Ciudadanía estadounidense

504

Firma del inventor [sigue una firma ilegible]

Fecha 27/3/02

Nombre PATT William Chester

Domicilio Chelsea, Michigan 48118, EE UU

Domicilio Postal 160 East Summit, Chelsea, Michigan
48118, EE UU

Ciudadanía estadounidense

Firma del inventor [sigue una firma ilegible]

Fecha 27/03/02

Nombre PHAM Ly

Domicilio Grand Rapids, Michigan 49507, EE UU

Domicilio Postal 1609 Buchanan SW, Grand Rapids,
Michigan 49507, EE UU

Ciudadanía estadounidense

Firma del inventor [sigue una firma ilegible]

Fecha 12/03/02

Formulario PCT/RO/101 (página de continuación para la
declaración) (marzo de 2001, reimpreso en enero de 2002)

Ver Notas al formulario de solicitud

Página No 11

Casillero No VIII (i) a (v) DECLARACIÓN

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Si el espacio no es suficiente en cualquiera de los Casilleros VIII (1) al (v) para proporcionar toda la información, incluyendo el caso en que se deban nombrar más de dos inventores en el Casillero VIII (iv), en tal situación, escribir "Continuación del Casillero No VIII" (indicar el número de ítem del casillero) y proporcionar la información del mismo modo que se requiere para los fines del Casillero en el cual el espacio resultó insuficiente. Si es necesario más espacio con respecto a dos o más declaraciones, se deberá usar un casillero de continuación separado para cada una de tales declaraciones. Si no se utiliza este casillero, esta página no deberá incluirse en la solicitud.

Nombre KOSTLAN Catherine Rose

Domicilio Saline, Michigan 48176, EE UU

Domicilio Postal 9876 Moon Road, Saline, Michigan 48176,
EE UU

Firma del inventor [sigue una firma ilegible]

Fecha 12/03/02

Nombre WILSON Michael William

Domicilio Ann Arbor, Michigan 48105

Domicilio Postal 3520 Charter Place, Ann Arbor, Michigan
48105

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Firma del inventor [sigue una firma ilegible]

Fecha 12/3/02

Formulario PCT/RO/101 (página de continuación para la declaración) (marzo de 2001, reimpreso en enero de 2002)

Ver Notas al formulario de solicitud

PCT/EP02/0197

Página No 12

Casillero No IX LISTA DE CONTROL IDIOMA DE PRESENTACION

Esta solicitud internacional contiene

(a) el siguiente número de páginas en papel

Solicitud (incluyendo las páginas de declaración)	12
Memoria descriptiva (excluyendo la parte del listado de secuencias)	202
Reivindicaciones	52
Resumen	1
Dibujos	
Subtotal del número de páginas	267

Listado de secuencias parte de la memoria descriptiva (numero real de páginas si se presentan en papel, ya sea que se presenten también en forma legible por computadora o no, ver (b) más abajo)

507

Número total de páginas

267

(b) listado de secuencias parte de la memoria descriptiva
presentada en forma legible por computadora

(1) ☐ solamente (conforme al artículo 801 (a) (i))

(11) ☐ además de ser presentado en papel (conforme
al artículo 801 (a) (ii))

Tipo y cantidad de portadores (diskette, CD-ROM, CD-R u
otro) en el que se guardó el listado de secuencias (las
copias adicionales se indican bajo el ítem 9(11), en la
columna de la derecha) ---

Esta solicitud internacional está acompañada por el/los
siguiente/s ítem/s (marcar el casillero que corresponda e
indicar en la columna de la derecha la cantidad de cada
ítem)

1 (X) Hoja de Calculo de Aranceles

2 () Poder original por separado

3 () Poder General original

4 () Copia del Poder General, número de referencia,
si lo hubiera ---

5 () Declaración explicando la falta de firma

6 (X) Documento/s de Prioridad identificados en
el Casillero No VI como ítem(s) ---

7 () Traducción de la Solicitud Internacional al

(idioma) ---

8 () Indicaciones por separado con respecto a
microorganismos depositados u otro material biológico

9 () Listado de secuencias en forma legible
por computadora (indicar también el tipo y cantidad de
portadores (diskette, CD-ROM, CD-R u otro))

(1) [] copia presentada para los fines de la
búsqueda internacional conforme a la norma 13ter
solamente (y no como parte de la solicitud
internacional)

(11) [] (sólo cuando se marque el casillero
(b) (1) o (b) (11) en la columna de la izquierda)
copias adicionales incluyendo, cuando corresponda,
la copia para los fines de la búsqueda internacional
conforme a la norma 13ter

(111) [] junto con una declaración relevante sobre
la identidad de la copia o copias con la parte del
listado de secuencias mencionado en la columna de
la izquierda

10 () Otros (especificar) ---

Figura de los dibujos que debe acompañar el resumen ---

Idioma de presentación de la solicitud internacional

Inglés

S/10

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Casillero No ☒ FIRMA DEL SOLICITANTE, AGENTE O REPRESENTANTE COMUN

Junto a cada firma, indicar el nombre de la persona que firma y el carácter en el cual lo hace (si dicho carácter no es obvio de la lectura de la solicitud)

[Aparece una firma ilegible debajo de la cual se lee]
HIRSCH Denise, Representante Profesional ante la Oficina Europea de Patentes

Para uso exclusivo de la Oficina receptora

- 1 Fecha del recibo real de la solicitud internacional de referencia 11 de febrero de 2002 (11 02 2002)
- 2 Dibujos recibido [], no recibido []
- 3 Fecha corregida de recepción real debido a papeles o dibujos recibidos más tarde pero en término y que completan la solicitud internacional de referencia ---
- 4 Fecha de la recepción en término de las correcciones solicitadas conforme al artículo 11(2) de PCT ---
- 5 Autoridad de Búsqueda Internacional (si dos o más son competentes) "ISA"/---
- 6 () Transmisión de la copia de la búsqueda retrasada hasta que se pague el arancel de búsqueda

Para uso exclusivo de la Oficina Internacional

Fecha de recepción de la copia de registro por parte de la
Oficina Internacional ---

Formulario PCT/RO/101 (última página) (marzo de 2001,
reimpreso en enero de 2002)

Ver notas al formulario de solicitud

PATENT COOPERATION TREATY

RECEIVED PCT/EP02/01979

21 JUN 2002 511

PCT

From the INTERNATIONAL BUREAU
Patents Fresnes

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24 2(a))

To

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

Date of mailing (day/month/year) 12 June 2002 (12 06 02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 018319 (A476) CD	International application No. PCT/EP02/01979

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below

Name(s) of the applicant(s) and State(s) for which they are applicants

WARNER-LAMBERT COMPANY (for all designated States except US)
ANDRIANJARA, Charles et al (for US)

International filing date 11 February 2002 (11 02 02)

Priority date(s) claimed 14 February 2001 (14 02 01)

Date of receipt of the record copy
by the International Bureau 30 April 2002 (30 04 02)

List of designated Offices

AP GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
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

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to

- ☒ time limits for entry into the national phase see updated important information (as of April 2002)
- ☐ confirmation of precautionary designations (if applicable)
- ☐ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Carlos NARANJO
Facsimile No. (41 22) 740.14.35	Telephone No. (41 22) 338.83.38

TRATADO DE COOPERACIÓN DE PATENTES

De la OFICINA INTERNACIONAL

RECIBIDO
21 de junio de 2002
PATENTES FRESNES

PCT

NOTIFICACIÓN DE RECEPCIÓN DE COPIA PARA REGISTRO

(PCT Disposición 24 2(a))

A

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

Fecha de envío (día/mes/año) 12 de junio de 2002 (12 06 02)	NOTIFICACIÓN IMPORTANTE						
Referencia del caso del Solicitante o del Apoderado 018319 (A478) CD	Número de Solicitud Internacional PCT/EP02/01979						
Se notifica en este acto al solicitante que la Oficina Internacional ha recibido la copia para registro de la solicitud internacional según se detalla a continuación Nombre(s) de(os) solicitante(s) y Estado(s) en los cuales son solicitantes WARNER LAMBERT COMPANY (en todos los estados designados excepto los Estados Unidos de América) ANDRIANJARA Charles y otros (en los Estados Unidos de América) <table><tr><td>Fecha de presentación internacional</td><td>11 de febrero de 2002 (11 02 02)</td></tr><tr><td>Fecha(s) de prioridad reivindicada(s)</td><td>14 de febrero de 2001 (14 02 01)</td></tr><tr><td>Fecha de recepción de la copia para registro por la Oficina Internacional</td><td>30 de abril de 2002 (30 04 02)</td></tr></table> Lista de Oficinas designadas AP GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW EA AM AZ BY KG KZ MD RU TJ TM EP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR OA BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG Nacional 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 ATENCIÓN El solicitante debe controlar cuidadosamente los datos que aparecen en esta Notificación. En caso de existir discrepancias entre estos datos y las indicaciones en la solicitud internacional el solicitante debe informar de inmediato a la Oficina Internacional Además, el solicitante debe prestar particular atención a la información contenida en el Anexo, con relación a		Fecha de presentación internacional	11 de febrero de 2002 (11 02 02)	Fecha(s) de prioridad reivindicada(s)	14 de febrero de 2001 (14 02 01)	Fecha de recepción de la copia para registro por la Oficina Internacional	30 de abril de 2002 (30 04 02)
Fecha de presentación internacional	11 de febrero de 2002 (11 02 02)						
Fecha(s) de prioridad reivindicada(s)	14 de febrero de 2001 (14 02 01)						
Fecha de recepción de la copia para registro por la Oficina Internacional	30 de abril de 2002 (30 04 02)						

5B

☒ los plazos para entrar a la fase nacional – ver información importante actualizada (a partir de abril de 2002) ☐ la confirmación de designaciones precautonas (si correspondiera) ☒ los requisitos en relación a los documentos de prioridad (si correspondiera) Una copia de esta Notificación se envía a la Oficina receptora y a la Autoridad de Búsqueda Internacional	
Oficina Internacional de la OMPI 34, chemin des Colombettes 1211 Geneva 20, Switzerland Número de fax: (41-22) 740 14 35	Funcionario autorizado Carlos NARANJO Número de teléfono (41-22) 338 83 38

PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To

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

Date of mailing (day/month/year) 12 June 2002 (12 06 02)	
Applicant's or agent's file reference 018319 (A476) CD	IMPORTANT NOTIFICATION
International application No PCT/EP02/01979	International filing date (day/month/year) 11 February 2002 (11 02 02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 14 February 2001 (14.02 01)
Applicant WARNER-LAMBERT COMPANY et al	

- 1 The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR" in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b).
- 2 This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3 An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 4 The letters "NR" appearing in the right hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17 1(a) or (b) respectively. In such a case, the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity upon entry into the national phase to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
14 Febr 2001 (14 02 01)	60/268,661	US	30 Apr 2002 (30 04 02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740 14.35	Authorized officer Carlos NARANJO Telephone No. (41-22) 338.83.38
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TRATADO DE COOPERACIÓN DE PATENTES

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De la OFICINA INTERNACIONAL

PCT

A.

NOTIFICACIÓN RELATIVA A LA PRESENTACIÓN O
TRANSMISIÓN DEL DOCUMENTO DE PRIORIDAD

(Instrucciones Administrativas del PCT Sección 411)

HIRSCH Denise
Pfizer Global Research and
Development
Fresnes Laboratories
3-9 rue de la Loge B P 100
F-94285 Fresnes Cedex
FRANCIA

Fecha de envío (día/mes/año)

12 de junio de 2002 (12 06 02)

Referencia del caso del Solicitante o del Apoderado

018319 (A476) CD

NOTIFICACIÓN IMPORTANTE

Número de Solicitud Internacional

PCT/EP02/01979

Fecha de Presentación Internacional (día/mes/año)

11 de febrero de 2002 (11 02 02)

Fecha de Publicación Internacional (día/mes/año)

No publicada aún

Fecha de Prioridad (día/mes/año)

14 de febrero de 2001 (14.02 01)

Solicitante

WARNER-LAMBERT COMPANY y otros

- 1 El solicitante queda por este acto notificado de la fecha de recepción (salvo que las letras "NR" aparezcan en la columna derecha) por parte de la Oficina Internacional del(os) documento(s) de prioridad relativo(s) a la(s) solicitud(es) anterior(es) indicadas más adelante. A menos que se indique lo contrario por un asterisco que aparezca al lado de la fecha de recepción o por las letras NR en la columna derecha el correspondiente documento de prioridad fue presentado o transmitido a la Oficina Internacional en cumplimiento de lo dispuesto en la Disposición 17 1(a) o (b).
- 2 La presente actualiza y reemplaza toda notificación anteriormente emitida con relación a la presentación o transmisión de los documentos de prioridad.
- 3 Un asterisco(*) al lado de la fecha de recepción en la columna derecha denota un documento de prioridad presentado o transmitido a la Oficina Internacional pero sin cumplir con lo establecido en la Disposición 17 1(a) o (b). En tal caso la atención del solicitante debe dirigirse a la Disposición 17 1(c) que establece que ninguna Oficina designada puede rechazar la reivindicación de prioridad sin antes dar al solicitante la posibilidad al entrar en la fase nacional de presentar el documento de prioridad dentro del plazo que sea razonable en virtud de las circunstancias.

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- 4 Las letras "NR" que aparezcan en la columna derecha denotan un documento de prioridad que no fue recibido por la Oficina Internacional o cuya preparación y transmisión a la Oficina Internacional el solicitante no solicitó a la Oficina receptora según lo dispuesto por la Disposición 17 1(a) o (b) respectivamente. En tal caso la atención del solicitante debe dirigirse a la Disposición 17 1(c) que establece que ninguna Oficina designada puede rechazar la reivindicación de prioridad sin antes dar al solicitante la posibilidad al entrar en la fase nacional de presentar el documento de prioridad dentro del plazo que sea razonable en virtud de las circunstancias.

Fecha de Prioridad

N° de Solicitud de Prioridad

País u Oficina regional u
Oficina receptora PCT

Fecha de recepción del
documento de prioridad

14 de febrero de 2001
(14 02 01)

60/268 661

US

30 de abril de 2002
(30 04 02)

Oficina Internacional de la OMPI
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Número de fax (41-22) 740 14 35

Funcionario autorizado

Carlos NARANJO

Número de teléfono (41-22) 338 83 38

PATENT COOPERATION TREATY

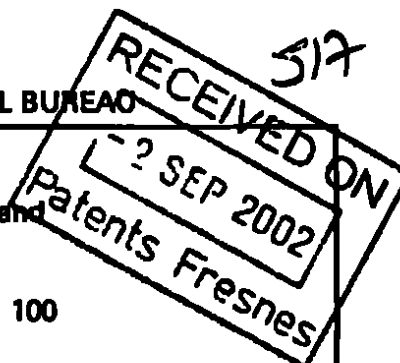
PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47 1(c), first sentence)

From the INTERNATIONAL BUREAU

To

HIRSCH, Denise
Pfizer Global Research and
Development
Fresnes Laboratoires
3-9, rue de la Loge, B P 100
F-94265 Fresnes Cedex
FRANCEDate of mailing (day/month/year)
22 August 2002 (22 08 02)Applicant's or agent's file reference
018319 (A476) CD

IMPORTANT NOTICE

International application No
PCT/EP02/01979International filing date (day/month/year)
11 February 2002 (11 02 02)Priority date (day/month/year)
14 February 2001 (14 02 01)

Applicant

WARNER-LAMBERT COMPANY et al

- 1 Notice is hereby given that the International Bureau has communicated, as provided in Article 20 the international application to the following designated Offices on the date indicated above as the date of mailing of this notice
KP, KR, US

In accordance with Rule 47 1(c) third sentence those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s)

- 2 The following designated Offices have waived the requirement for such a communication at this time

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, 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

The communication will be made to those Offices only upon their request. Furthermore those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a bis))

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on
22 August 2002 (22 08 02) under No. WO 02/064572

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase

The applicable time limit for entering the national phase will subject to what is said in the following paragraph be 30 MONTHS from the priority date not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date but also in respect of any designated Office in the absence of filing of such demand where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office For further details, see PCT Gazette No. 44/2001 of 1 November 2001 pages 19928 19932 and 19934 as well as the PCT Newsletter October and November 2001 and February 2002 issues

In practice time limits other than the 30-month time limit will continue to apply for various periods of time, in respect of certain designated or elected Offices For regular updates on the applicable time limits (20 21, 30 or 31 months or other time limit) Office by Office refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide Volume II National Chapters, all available from WIPO's Internet site at <http://www.wipo.int/pct/en/index.html>

For filing a demand for international preliminary examination, see the PCT Applicant's Guide Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20 Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J Zahra

Telephone No. (41-22) 338 91 11

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

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Date of mailing (day/month/year) 22 August 2002 (22 08 02)	IMPORTANT NOTICE
Applicant's or agent's file reference 018319 (A476) CD	International application No. PCT/EP02/01979
The applicant is hereby notified that, at the time of establishment of this Notice the time limit under Rule 48.1 for making amendments under Article 18 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.	

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WO 02/084572
PCT/EP02/01979

TRATADO DE COOPERACIÓN DE PATENTES

De la Oficina Internacional

PCT

RECIBIDO
02 de septiembre de 2002
PATENTES - FRESNES

NOTIFICACIÓN POR LA QUE SE INFORMA AL SOLICITANTE
SOBRE LA COMUNICACIÓN DE LA SOLICITUD INTERNACIONAL
A LAS OFICINAS DESIGNADAS

(PCT Disposición 47 1(c) primera parte)

A.
HIRSCH Denise
Pfizer Global Research and
Development
Fresnes Laboratoires
3-9 rue de la Loge B P 100
F-94285 Fresnes Cedex
FRANCIA

Fecha de envío (día/mes/año) 22 de agosto de 2002 (22 08 02)		
Referencia del caso del Solicitante o del Apoderado 018319 (A478) CD		NOTIFICACIÓN IMPORTANTE
Número de Solicitud Internacional PCT/EP02/01979	Fecha de Presentación internacional (día/mes/año) 11 de febrero de 2002 (11 02 02)	Fecha de prioridad (día/mes/año) 14 de febrero de 2001 (14 02 01)
Solicitante WARNER LAMBERT COMPANY y otros		
1 Por la presente se notifica que la Oficina Internacional ha comunicado según lo dispuesto en el Artículo 20 la solicitud internacional a las siguientes Oficinas designadas en la fecha indicada anteriormente como fecha de envío de la presente notificación KP KR US En virtud de la Disposición 47 1(c) tercera parte esas Oficinas aceptarán la presente notificación como prueba concluyente de que la comunicación de la solicitud internacional se ha efectuado en la fecha de envío indicada anteriormente y no se requiere la presentación por parte del solicitante de una copia de la solicitud internacional a la(s) Oficina(s) designada(s) 2 Las siguientes Oficinas designadas han renunciado por el momento a la exigencia de esta comunicación AE AG AL AM AP AT AU AZ BA BB BG BR BY, BZ CA, CH CN, CO, CR CU CZ DE DK, DM DZ EA EC EE EP ES FI GB GD, GE GH GM HR HU ID IL, IN IS JP KE KG KZ LC LK LR LS LT LU LV MA, MD MG MK MN MW, MX, MZ, NO, NZ OA, 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 Esta comunicación se realizará a estas Oficinas sólo si fuera solicitada Además estas Oficinas no exigen que el solicitante presente una copia de la solicitud internacional (Disposición 49 1(a-bis)) 3 Se adjunta a la presente notificación una copia de la solicitud internacional como fue publicada por la Oficina Internacional el 22 de agosto de 2002 (22 08 02) bajo el número WO 02/084572		

PLAZOS para la presentación de un pedido de examen preliminar internacional y para entrar en la fase nacional

El plazo aplicable para entrar a la fase nacional será sujeto a lo previsto en el párrafo siguiente, de 30 MESES a partir de la fecha de prioridad no sólo con respecto a cualquier Oficina elegida al se presenta un pedido de examen preliminar internacional antes del vencimiento del término de 19 meses desde la fecha de prioridad sino también con respecto a cualquier Oficina designada en ausencia de la presentación de tal pedido el Artículo 22(1) con sus modificaciones vigente desde el 1° de abril de 2002 es de aplicación con respecto a la Oficina designada

Para mayor información ver la Gaceta del PCT N° 44/2001 del 1° de noviembre de 2001 páginas 19928 19932 y 19934 como así también el Boletín Informativo del PCT ediciones de octubre y noviembre de 2001 y febrero de 2002

En la práctica los plazos distintos del plazo de 30 meses continuarán siendo de aplicación por distintos periodos con respecto a ciertas Oficinas designadas o elegidas Para obtener información sobre actualizaciones regulares de los plazos aplicables (20 21, 30 ó 31 meses u otro plazo) Oficina por Oficina referirse a la Gaceta del PCT el Boletín Informativo del PCT y la Guía del Solicitante PCT Tomo II Capítulos Nacionales todos disponibles en la página de Internet de la OMPI, en <http://www.wipo.int/pct/en/index.html>

Por la presentación de un pedido de examen preliminar internacional, ver la Guía del Solicitante PCT Tomo I/A Capítulo IX Únicamente un solicitante que es nacional o residente de un Estado Contratante del PCT vinculado por el Capítulo II tiene derecho a presentar un pedido de examen preliminar internacional (actualmente todos los Estados Contratantes del PCT están vinculados por el Capítulo II)

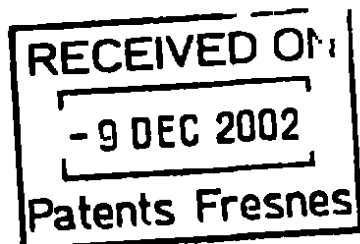
Es de exclusiva responsabilidad del solicitante controlar todos los plazos

Oficina Internacional de la OMPI 34 chemin des Colombettes 1211 Geneva 20 Switzerland Número de fax (41-22) 740 14 35	Funcionario autorizado J ZAHRA Número de teléfono (41 22) 338 91 11
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Continuación del Formulario PCT/IB/308

NOTIFICACIÓN POR LA QUE SE INFORMA AL SOLICITANTE SOBRE LA COMUNICACIÓN DE LA SOLICITUD INTERNACIONAL A LAS OFICINAS DESIGNADAS

Fecha de envío (día/mes/año) 22 de agosto de 2002 (22 08 02)	NOTIFICACIÓN IMPORTANTE
Referencia del caso del Solicitante o del Apoderado 018319 (A476) CD	Número de Solicitud Internacional PCT/EP02/01979
Por la presente se notifica al solicitante que al momento de emitirse esta Notificación el plazo establecido por la Disposición 46 1 para la realización de modificaciones en conformidad con el Artículo 19 todavía no había vencido y que la Oficina Internacional no había recibido tales modificaciones como así tampoco ninguna declaración del solicitante en el sentido de que no desea realizar modificaciones	



PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL BUREAU

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To

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

Date of mailing (day/month/year) 24 November 2002 (24 11 02)		IMPORTANT INFORMATION	
Applicant's or agent's file reference 018319 (A476) CD			
International application No. PCT/EP02/01979	International filing date (day/month/year) 11 February 2002 (11 02 02)	Priority date (day/month/year) 14 February 2001 (14 02 01)	
Applicant WARNER-LAMBERT COMPANY et al			

- 1 The applicant is hereby informed that the International Bureau has, according to Article 31(7) notified each of the following Offices of its election

EP AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
National AU,BG,CA,CN,DE,GB,IL,JP,KP,KR,MN,NO,PL,RO,RU,SK,US

- 2 The following Offices have waived the requirement for the notification of their election the notification will be sent to them by the International Bureau only upon their request

AP GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW
EA AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
OA BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National AE,AG,AL,AM,AT,AZ,BA,BB,BR,BY,BZ,CH,CO,CR,CU,CZ,DK,DM,DZ,EC,EE,
ES,FI,GD,GE,GH,GM,HR,HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,
MK,MW,MX,MZ,NZ,OM,PH,PT,SD,SE,SG,SI,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,UZ,VN,YU,
ZA,ZM,ZW

- 3 The applicant is reminded that he must enter the national phase before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)) as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1)

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office see Volume II of the PCT Applicant's Guide

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Farid ABBOU
Facsimile No. (41-22) 740.14.35	Telephone No. (41 22) 338.83.38

TRATADO DE COOPERACION EN MATERIA DE PATENTES**PCT/EP02/01979****PCT****INFORMACIÓN SOBRE LAS OFICINAS ELEGIDAS NOTIFICADAS SOBRE SU
ELECCION****(Norma PCT 61 3)****Desde la OFICINA INTERNACIONAL****A HIRSCH, Dense****Pfizer Global Research and****Development****Fresnes Laboratories****3-9, rue de la Loge, B P 100****F-94265 Fresnes Cedex****Francia****[Aparece un sello que reza] RECIBIDO el 9 de diciembre de 2002****Patentes Fresnes****NOTIFICACION IMPORTANTE**

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Fecha de correspondencia (día/ mes/ año) 24 de noviembre de 2002
(24-11-2002)

Archivo de referencia del agente o solicitante 018319 (A476) CD

Solicitud Internacional No PCT/EP02/01979

Fecha de presentación internacional (día/ mes/ año) 11 de
febrero de 2002 (11/02/2002)

Fecha de Prioridad (día/ mes/ año) 14 de febrero de 2001
(14/02/2001)

Solicitante WARNER- LAMBERT COMPANY et al

1 Por medio de la presente se informa al solicitante que la
Oficina Internacional ha, de acuerdo con el Inciso 31(7),
notificado sobre su elección a las siguientes oficinas

EP AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, TR

Nacional AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL,
RO, RU, SK, US

2 Las siguientes oficinas han renunciado al pedido de notificación de su elección, la notificación les será enviada por la Oficina Internacional solo si lo solicitan

AP GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

Nacional AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

3 Se recuerda al solicitante que debe entrar a la "fase nacional" **antes de los 30 meses desde la fecha de prioridad** ante cada una de las Oficinas anteriormente listadas. Debe realizarse abonando los aranceles nacionales y entregando, si se requiere, una traducción de la solicitud internacional (inciso 39(1)), así como también, cuando sea necesario, una traducción de cualquier anexo del informe de examen preliminar internacional (Inciso 36(3)(b) y Norma 74 1)

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Algunas oficinas tienen límites de tiempo fijados que vencen después del anteriormente mencionado Para más información sobre límites de tiempo aplicables y los hechos a realizarse para entrar a la fase nacional ante cualquier Oficina Particular, véase Volumen II de la Guía del Solicitante de PCT

La entrada a la fase regional Europea se pospone hasta los 31 meses desde la fecha de prioridad en todos los Estados designados para obtener una Patente Europea

La Oficina Internacional de WIPO

34, chemin des Colombettes

1211 Génova 20, Suiza

Fax No (41-22) 740 14 35

Funcionario Autorizado Farid ABBOU

Tel No (41-22) 338 83 38

Formulario PCT/IB/332 (septiembre de 1997)

RECEIVED ON
24 JUN 2002
PGT
Patents, Fresno
527

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION**

(PCT Rule 44.1)

FOR FURTHER ACTION See paragraphs 1 and 4 below

International filing date
(day/month/year) 11/02/2002

WARNER-LAMBERT COMPANY

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

Véronique Baillou

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01979

528

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/96 C07D401/12 C07D405/12 C07D409/12 C07D405/14
C07D409/14 C07D471/04 C07D403/12 C07D403/10 C07D401/10
C07D413/10 C07D401/06 A61K31/5025 A61K31/505

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

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)

WPI Data, PAJ, BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
(14) X	LIVERTON N J ET AL "Nonpeptide glycoprotein IIB/IIIa inhibitors substituted quinazolinones and quinazolinones as potent fibrinogen receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol 8, no 5, 3 March 1998 (1998-03-03), pages 483-486, XP004136889 ISSN 0960-894X see compound 7 page 481	17,18
(15) X	H OGAWA ET AL "Studies on positive inotropic agents V" CHEM PHARM BULL, vol 36, no 6, 1988, pages 2253-2258, XP001080174 see compound X chart I	17,18
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents

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

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

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

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

& document member of the same patent family

Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

25/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 6818 Patentlaan 2
NL - 2260 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 apo nl,
Fax (+31-70) 340-3018

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01979

529

530

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 ^{///}(C07D471/04,239 00,221 00)

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)

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS,OHIO,US, XP002201020 ORDER NO A1240/0056923 & "SCREENING COLLECTION" 28 March 2000 (2000-03-28) , ZELINSKY INSTITUTE OF ORGANIC CHEMISTRY , 47 LENINSKY PROSPECT, MOSCOW, 117913 RUSSIA -/--	1

☒ Further documents are listed in the continuation of box C.

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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
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- "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
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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentstein 2
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Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01979

530

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
(2) X,P	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201021 ORDER NOS CHS 1938401 CHS 1938397 CHS 1938395 & "CHEMSTAR PRODUCT LIST" 16 May 2001 (2001-05-16), CHEMSTAR LTD , LENINGRADSKII PROSPECT 47, OFFICE 465, MOSCOW,125167 RUSSIA	1
(3) P,X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201022 ORDER NOS STOCKIN-2756, A1336/0060317, STOCKIS-85693, STOCKIS-77305, STOCKIS-81043, STOCKIS-82046 & "AMBINTER EXPLORATORY LIBRARY" 21 January 2002 (2002-01-21), AMBINTER , 46 QUAI LOUIS BLERIoT, PARIS, F-75016, FRANCE	1
(4) P,X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201023 ORDER NOS C-055658, C-055656, Z-007159, Z-007158, C-055659 & "SCIENTIFIC EXCHANGE PRODUCT LIST" 1 June 2001 (2001-06-01), SCIENTIFIC EXCHANGE, INC, PINE RIVER ROAD, PO BOX 918, CENTER OSSIPPEE, NH 03814, USA	1
(5) X	CHEMICAL ABSTRACTS, vol 54, no 3, 10 February 1960 (1960-02-10) Columbus, Ohio, US, abstract no 2375e, NESTEROV XP002201019 abstract & SU 119 879 A (NESTEROV ET AL) 21 May 1959 (1959-05-21) Compound pyrimido'5,4-d'pyrimidine-2,4(1H,3H)-dione , 6-(benzylthio)-, RN 100382-60-3 -/-	1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01979

531

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
(6) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, MURATA, SHIZUAKI ET AL "Regioselective synthesis of 6-substituted lumazines by using highly reactive lumazine 6-triflate" retrieved from STN Database accession no 128 243870 XP002201024 abstract & CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 17-22 EDITOR(S) PFLEIDERER, WOLFGANG ROKOS, HARTMUT PUBLISHER BLACK, compound RN 191275-58-8	1
(X) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, KIM, YEONHEE ET AL "Side chain reactions of 6-acetyl-1,3,7-trimethylumazine" retrieved from STN Database accession no 128 243871 XP002201025 abstract & CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 41-44 EDITOR(S) PFLEIDERER, WOLFGANG ROKOS, HARTMUT PUBLISHER BLACK, compound RN 109879-41-6	1
(Cb) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, ABOU-HADEED, KHALED ET AL "Pteridines CVIII Reactions of 6,7-dichloro-1,3-dimethylumazine with sulfur nucleophiles" retrieved from STN Database accession no 126 212115 XP002201026 compound RN 188023-01-0 abstract & PTERIDINES (1996), 7(4), 113-122 , --- -/-	1

Form PCT/BA/E10 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01979

532

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
(S) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, SLADOWSKA, H ET AL "Synthesis and properties of amides of 1-benzyl-3-methyl- and 1-butyl-3-phenyl-7-methyl-4-oxo-2-thioxo (2,4-dioxo)-1,2,3,4-tetrahydropyrido'2,3-d'pyrimidine-6-carboxylic acids" retrieved from STN Database accession no 107 58977 XP002201027 compounds 109493-30-3 and 109493-25-6 abstract & FARMACO, ED SCI (1986), 41(12), 954-63	1,29
(CP) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, LESPAGNOL, ALBERT ET AL "Study on antifolic agents 1 Derivatives of 4-nitrobenzene-1,3- dicarboxylic acid" retrieved from STN Database accession no 87 152121 XP002201028 compound RN 64152-16-5 abstract & BULL SOC PHARM LILLE (1977), 33(1), 67-77	1
(A) X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, GHOSE, ARUP K ET AL "A general distance-geometry three-dimensional receptor model for diverse dihydrofolate reductase inhibitors" retrieved from STN Database accession no 101 16805 XP002201029 compound RN 52979-05-2 and 52979-04-1 abstract & J MED CHEM (1984), 27(7), 901-14	1,29
(M) X	DE 24 41 959 A (CIBA GEIGY AG) 13 March 1975 (1975-03-13) compound rn 56044-13-4, Piperidine,1-'(1,2,3,4-tetrahydro-2,4-dioxo-6-quinazoliny)sulfonyl'	1
1	-/-	

Form PCT/BAE10 (continuation of extended sheet) (July 1982)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/01979

533

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
13 X	WO 99 64400 A (BEMIS GUY , VERTEX PHARMA (US), COCHRAN JOHN (US), SALITURO FRANCES) 16 December 1999 (1999-12-16) see general formula and page 5, lines 17-end	1-39
14 A	REITER L A ET AL "Inhibition of MMP-1 and MMP-13 with phosphinic acids that exploit binding in the S2 pocket" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol 9, no 2, 18 January 1999 (1999-01-18), pages 127-132, XP004152585 ISSN 0960-894X the whole document	1-39
15 A	CHEN J M ET AL "STRUCTURE-BASED DESIGN OF A NOVEL, POTENT, AND SELECTIVE INHIBITOR FOR MMP-13 UTILIZING NMR SPECTROSCOPY AND COMPUTER-AIDED MOLECULAR DESIGN" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol 122, 2000, pages 9648-9654, XP001010185 ISSN 0002-7863 the whole document	1-39
16 A	WO 97 43239 A (BRITTELLI DAVID R , ZANDT MICHAEL C VAN (US), DIXON BRIAN R (US), B) 20 November 1997 (1997-11-20) the whole document	1-39

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/01979

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

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

- 1 ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority namely:
Although claims 35-39 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

Information on patent family members

International Application No

PCT/EP 02/01979

535

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
SU 119879	A	NONE	
DE 2441959	A	13-03-1975	
		AU 7296174 A	11-03-1976
		DE 2441959 A1	13-03-1975
		DK 408574 A	05-05-1975
		FR 2243195 A1	04-04-1975
		NL 7411179 A	10-03-1975
		OA 4773 A	31-08-1980
		SE 7410216 A	07-03-1975
		BE 819580 A1	05-03-1975
		JP 50050390 A	06-05-1975
WO 9964400	A	16-12-1999	
		AU 4429799 A	30-12-1999
		EP 1086085 A1	28-03-2001
		WO 9964400 A1	16-12-1999
		US 2001025044 A1	27-09-2001
WO 9743239	A	20-11-1997	
		AU 714207 B2	23-12-1999
		AU 3122097 A	05-12-1997
		BR 9709086 A	03-08-1999
		CA 2254731 A1	20-11-1997
		CN 1225621 A	11-08-1999
		EP 0923530 A1	23-06-1999
		HR 970244 A1	30-04-1998
		JP 11510821 T	21-09-1999
		WO 9743239 A1	20-11-1997
		ZA 9704030 A	19-02-1998

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES**PCT**

**NOTIFICACIÓN DE LA TRANSMISIÓN DEL INFORME DE BÚSQUEDA
INTERNACIONAL O LA DECLARACIÓN**

(PCT, Norma 44 1)

**[en el margen superior derecho aparece un sello que reza]
RECIBIDO EL 24 DE JUNIO DE 2002 PATENTES, FRESNES**

De la AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Para

PFIZER

Global Research and Development

Atención Hirsch, Denise

3-9 rue de la Loge, B P 100

F-94265 Fresnes Cedex

Francia

Fecha de envío (día/mes/año) 25/06/2002

Referencia del archivo del Solicitante o Agente 018319 (A476)

CD

PARA OTROS TRAMITES ver párrafos 1 y 4, más abajo

Solicitud Internacional No PCT/EP 02/01979

Fecha de Presentación internacional (día/mes/año) 11/02/2002

Solicitante WARNER-LAMBERT COMPANY

1 [x] Por la presente se notifica al solicitante que el informe de búsqueda internacional se ha establecido y transmitido con la presente

Presentación de modificaciones y alegato conforme a la Cláusula 19

El solicitante tiene derecho, si lo desea, de modificar las reivindicaciones de la solicitud internacional (véase la Norma 46)

¿Cuándo? El plazo para presentar dichas modificaciones es normalmente de 2 meses desde la fecha de transmisión del informe de búsqueda internacional, sin embargo, para obtener más detalles, ver las notas en la página adjunta

¿Dónde? Directamente a la Oficina Internacional de la OMPI

34, chemin des Colombettes

1211 Ginebra 20, Suiza

Fax (41-22) 740 14 35

Para obtener instrucciones más detalladas, ver las notas en la página adjunta

2 [] Por la presente se notifica al solicitante que no se establecerá informe de búsqueda internacional y que la declaración conforme al Artículo 17(2)(a) a tal efecto se transmite con la presente

3 [] Con respecto a la protesta contra el pago de (un) arancel(es) adicionales conforme a la Norma 40 2, se notifica al solicitante que

[] la protesta así como la resolución sobre ella ha sido transmitida a la Oficina Internacional junto con el pedido del solicitante de remitir los textos de la protesta y de la resolución sobre ella a las Oficinas designadas

[] aún no ha habido resolución sobre la protesta, el solicitante será notificado en cuanto haya una resolución

4 Otro(s) trámite(s) Se recuerda al solicitante que

Poco después de los 18 meses desde la fecha de prioridad, la Oficina Internacional publicará la solicitud internacional Si el solicitante desea evitar o postergar la publicación, un escrito de retiro de la solicitud internacional, o de la reivindicación de prioridad, deberán ser presentados ante la Oficina Internacional según lo previsto en las Normas 90bis 1 y 90bis 3, respectivamente, antes de la finalización de los preparativos técnicos para la publicación internacional

Dentro de los 19 meses desde la fecha de prioridad, deberá presentarse un pedido de examen preliminar internacional si el solicitante desea postergar el ingreso en la fase nacional

hasta los 30 meses desde la fecha de prioridad (en algunas Oficinas mas)

Dentro de los 20 meses desde la fecha de prioridad, el solicitante deberá realizar los trámites previstos para el ingreso en la fase nacional ante todas las Oficinas designadas que no hayan sido elegidas dentro de los 19 meses desde la fecha de prioridad o que no pudieran elegirse porque no se rigen por el Capítulo II

Nombre y domicilio para correspondencia de la Autoridad de Búsqueda Internacional

Oficina de Patentes Europea, P B 5818 Patentlaan 2

NL-2280 HV Rijswijk

Tel (+31-70)340-2040, Tx 31 651 epo nl,

Fax (+31-70)340-3016

Funcionario Autorizado Véronique Baillou

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/EP 02/01979

A Clasificación de la Materia

IPC 7 C07D239/96	C07D401/12	C07D405/12	C07D409/12
C07D405/14	C07D409/14	C07D471/04	C07D403/12
C07D403/10	C07D401/10	C07D413/10	C07D401/06
A61K31/5025	A61K31/5025	A61K31/505	

De acuerdo con la Clasificación Internacional de Patentes (IPC) o con la clasificación nacional e IPC

B Campos de Búsqueda

Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación)

IPC 7 C07D A61K

Documentación buscada además de la documentación mínima en la medida en que tales documentos están incluidos en los campos de búsqueda

[en blanco]

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda usados)

WPI Data, PAJ, BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C Documentos Considerados Relevantes

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
X	LIVERTON N J ET AL "Inhibidores no péptidos de la glucoproteína Iib/IIIa quinazolinonas y quinazolindionas como potentes antagonistas receptores de fibrinogeno" [del inglés <i>Nonpeptide glycoprotein Iib/IIIa inhibitors substituted quinazolinediones and quinazolinones as potent fibrinogen receptor antagonists</i>] BIOOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, Vol 8, no 5, 3 de marzo de 1998 (1998-03-03), Páginas 483-486, XP004136889 SIN 0960-894X Véase el compuesto 7 en la página 481 ---	17, 18
X	H OGAWA ET AL "Estudios sobre agentes V intotrópicos" [del inglés, <i>Studies</i>	17,18

	on positive intotropic agents V] CHEM PHARM BULL, Vol 36, no 6, 1998, páginas 2253-2258, XP001080174 Véase el compuesto X del gráfico I --- -/--	
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[x] Se mencionan otros documentos en la continuación del Casillero C

[x] En el anexo se enumeran miembros de familia de patentes

* Categorías especiales de documentos citados

"A" documento que define el estado general del arte que no se considera de particular relevancia

"E" documento anterior pero publicado en la fecha de presentación internacional o con posterioridad a ella

"L" documento que puede arrojar dudas sobre la reivindicación de prioridad o que se cita para establecer la fecha de publicación de otra cita o por otra razón especial (especificada)

"O" documento que refiere a una revelación oral, uso, exhibición u otro medio

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada

"T" documento posterior publicado con posterioridad a la fecha de presentación internacional o a la fecha de prioridad y que no está en conflicto con la solicitud pero citado para comprender un principio o teoría que sustenta la invención

"X" documento de particular relevancia la invención reivindicada no puede considerarse nueva o no puede considerarse que implica un paso inventivo cuando el documento se toma solo

"Y" documento de particular relevancia la invención reivindicada no puede considerarse que implica un paso inventivo cuando el documento se combina con otro u otros documentos, siendo dicha combinación obvia para un experto en el arte

"g" documento miembro de la misma familia de patentes

Fecha de la finalización efectiva de la búsqueda internacional 4 de junio de 2002

Fecha de envío del informe de búsqueda internacional 25/06/02

Nombre y domicilio de la ISA

Oficina de Patentes Europea, P B 5818 Patentlaan 2

NL-2280 HJ Rijswijk

Tel (31-70)340-2040 Tx 31 651 epo nl,

Fax (31-70)340-3016

Funcionario autorizado Scruton-Evans, I

Formulario PCT/ISA/210 (página dos) (julio de 1992)

página 1 de 6

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional No PCT/EP 02/01979

A Clasificación de la Materia

IPC 7 // (C07D471/04, 239 00, 221 00)

De acuerdo con la Clasificación Internacional de Patentes (IPC) o con la clasificación nacional e IPC

B Campos de Búsqueda

Documentación mínima buscada (sistema de clasificación seguido por símbolos de clasificación)

[en blanco]

Documentación buscada además de la documentación mínima en la medida en que tales documentos están incluidos en los campos de búsqueda

[en blanco]

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda usados)

[en blanco]

C Documentos Considerados Relevantes

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
P,X	BASE DE DATOS CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE COLUMBUS, OHIO, US, XP002201020 No DE ORDEN A1240/0056923 & "SCREENING COLLECTION" 28 de marzo de 2000 (2000-03-28), ZELINSKI INSTITUTE OF ORGANIC CHEMISTRY, 47 PERSPECTIVA LENINSKI, MOSCU, 117913 RUSIA --- -/--	1

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54A

documentos, siendo dicha combinación obvia para un experto en el arte

"&" documento miembro de la misma familia de patentes

Fecha de la finalización efectiva de la búsqueda internacional 4 de junio de 2002

Fecha de envío del informe de búsqueda internacional

Nombre y domicilio de la ISA

Oficina de Patentes Europea, P B 5818 Patentlaan 2

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Funcionario autorizado Scruton-Evans, I

Formulario PCT/ISA/210 (página dos) (julio de 1992)

página 2 de 6

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional N° PCT/EP 02/01979

C (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
X,P	BASE DE DATOS CHEMICATS Online'	1

	CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201021 No DE ORDEN CHS 1938401 CHS 1938397 CHS 1938395 & "CHEMSTAR PRODUCT LIST" 16 de mayo de 2001 (2001-05-16), CHEMSTAR LTD, PERSPECTIVA 47 LENINGRADISKII, OFICINA 465, MOSCU, 125167 RUSIA ---	
P,X	BASE DE DATOS CHEMCATS Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201022 Nos DE ORDEN STOCKIN-2756, A1336/0060317, STOCKIS-85693, STOCKIS- 77305, STOCKIS-81043, STOCKIS-82046 & "AMBINTER EXPLORATORY LIBRARY" 21 de enero de 2002 (2002-01-21), AMBINTER, 46 QUAI LOUIS BLEROT, PARIS, F-75016, FRANCIA ---	1
P,X	BASE DE DATOS CHEMCATS Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS,	1

~~880~~
549

	OHIO, US, XP002201023 Nos DE ORDEN C-055658, C-55656, Z-- 007159, Z-007158, C055659 & "SCIENTIFIC EXCHANGE PRODUCT LIST" 1 de junio de 2001 (2001-06-01), SCIENTIFIC EXCHANGE, INC, PINE RIVER ROAD, PO BOX 918, CENTER OSS�PEE, NH 03814, EUA ---	
X	CHEMICAL ABSTRACTS, vol 54, No 3, 10 de febrero de 1960 (1960-02-10) Columbus, Ohio, US, Resumen No 2375e, NESTEROV XP002201019 Resumen & SU 119 879 A (NESTEROV ET AL) 21 de mayo de 1959 (1959-05-21) Compuesto pirimido 5,4-d'pirimidina- 2,4(1H,3H)-diona, 6-(benciltio) [del inglés Compound pyrimido 5,4- d'pyrimidine-2,4(1H,3H)-dione, 6- (benzylthio)]-, RN 100382-60-3	1

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Formulario PCT/ISA/210 (continuación de la segunda página) (julio de 1992)

página 3 de 6

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional N° PCT/EP 02/01979

C (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
X	BASE DE DATOS CA Online¹ CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, MURATA, SHIZUAKI ET AL Síntesis regioselectiva de lumacinas 6-sustituidas mediante lumacina 6-triflato altamente selectiva" [del inglés <i>Regioselective synthesis of 6-substituted lumazines by using highly</i>	1

	reactive lumazine 6-triflate" Recuperado de STN No de acceso a base de datos 128 243870 XP002201024 Resumen & CHEMISTRY AND BIOLOGY OF PTERIDINES AND FLOATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, ALEMANIA, JUNIO 15-20, 1997 (1997), 17-22 EDITOR(ES) PFLEIDERER, WOLFGANG ROKOS, HARTMUT EDITORIAL BLACK, Compuesto RN 191275-58-8 ---	
x	BASE DE DATOS CA Online SERVICIO RESUMENES DE QUÍMICA, COLUMBUS, OHIO, US, KIM, YEONHEE ET AL "Reacciones de cadena lateral de 6-acetil-1, 3,7-trimetillumacina" [del inglés Side	1

552

Chain reactions of 6-acetyl-1, 3,7-trimethylumazine]

Recuperado de STN

No de acceso a la base de datos

128 243871

XP002201025

resumen

& CHEMISTRY & BIOLOGY OF PTERIDINES
AND FOLATES 1997, PROCEEDINGS OF THE
INTERNATIONAL SYMPOSIUM ON PTERIDINES
AND FOLATES, 11TH, BERCHTESGADEN,
ALEMANIA,

JUNIO 15-20, 1997 (1997), 41-44

EDITOR(ES) PFLEIDERER, WOLFGANG

ROKOS, HARTMUT

EDITORIAL BLACK,

Compuesto No RN 109879-41-6

X

BASE DE DATOS CA Online'

1

CHEMICAL ABSTRACTS SERVICE, COLUMBUS,
OHIO, US,

ABOU-HADEED, KHALED ET AL "Pteridinas

CVIII Reacciones de 6,7-dicloro1,3-

553

dimetillumacina con nucleófilos de
 azufre" [del inglés *Pteridines CVIII*
Reactions of 6,7-dichloro-1,3-
dimethylumazine with sulfur
nucleophiles]

recuperado de STN

No de acceso a la base de datos

126 212115

XP0220126

compuesto RN 188023-01-0

resumen

& PTERIDINES (1996), 7(4), 113-122,

Formulario PCT/ISA/210 (continuación de la segunda página)

(julio de 1992)

página 4 de 6

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional N° PCT/EP 02/01979

C (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la
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		reivindica ción N°
X	BASE DE DATOS CA Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, SLADOWSKA, H ET AL "Síntesis y propiedades de amidas de ácidos 1- bencil-3-metil-y 1-butil-3-fenil-7-metil-4-oxo-2- tioxo(2,4-dioxo)-1,2,3,4- tetrahidropirido 2,3-d'pirimidina-6- carboxílicos" [del inglés <i>Synthesis and properties of amides of 1-benzyl-3- methyl-and 1-butyl-3-phenyl-7-methyl-4-oxo-2- thioxo(2,4-dioxo)-1,2,3,4- tetrahydropyrido 2,3-d'pyrimidine-6- carboxylic acids</i>] recuperado de STN No de acceso ala base de datos 107 58977 XP002201027 Compuestos 109493-30-3 y 109493-25-6 Resumen	1,29

	& FÁRMACO, ED SCI (1986), 41(12), 954-63 ---	
X	BASE DE DATOS CA Online CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, LESPAGNOL, ALBERT ET AL "Estudio de agentes antifólicos 1 Derivados del ácido 4-nitrobenceno-1,3-dicarboxílico [del inglés, <i>Study on antifolic agents 1 Derivatives of 4-nitrobenzene-1,3-dicarboxylic acid</i>] recuperado de STN No de acceso a la base de datos 87 152121 XP002201028 Compuesto RN 64152-16-5 Resumen & BULL SOC PHARM LILLE (1997), 33(1), 67-77, ---	1
X	BASE DE DATOS CA Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US,	1,29

556

	GHOSE, ARUP K ET AL " Un modelo de receptor tridimensional distancia-geometria para distintos inhibidores de la reductasa dihidrofolato" [del inglés <i>A general distance-geometry three-dimensional receptor model for diverse dihydrofolate reductase inhibitors</i>] recuperado de STN No de acceso a la base de datos 101 16805 XP002201029 compuesto RN 52979-05-2 y 52979-04-1 resumen & J MED CHEM (1984), 27(7), 901-14, ---	
X	DE 24 41 959 A (CIBA GEIGY AG) 13 de marzo de 1975 (1975-03-13) compuesto rn 56044-13-4, Piperidine ,1- (1,2,3,4-tetrahydro-2,4-dioxo-6-quinazolinyl)sulfonyl' --- -/--	1

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INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional N° PCT/EP 02/01979

C (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Cita de documento, indicando, si corresponde, los pasajes relevantes	Relevante para la reivindicación N°
X	WO 99 64400 (BEMIS GUY, VERTEX PHARMA (US), COCHRAN JOHN (US), SALITURO FRANCES) 16 de diciembre de 1999 (1999-12-16) véase la fórmula general y la página 5, líneas 17 hasta el final ---	1-39
A	REITER L A ET AL "Inhibición de la MMP-1 y MMP-13 con ácidos fosfínicos que estallan y se unen en el espacio sacular S2 [del inglés <i>Inhibition of MMP-1 and MMP-13 with phosphinic acids that exploit binding in the S2 pocket</i> "] BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB,	1-39

558

Vol 9, No 2,
18 de enero de 1999 (1999-01-18),
páginas 127-132, XP00412585
SIN 0960-894X

El documento completo

A CHEN J M ET AL "DISEÑO CON BASE EN LA 1-39
ESTRUCTURA DE UN INHIBIDOR DE MMP-13
NOVEDOSO, POTENTE Y SELECTIVO QUE
UTILIZA ESPECTROSCOPIA DE RMN Y DISEÑO
MOLECULAR COMPUTARIZADO" [del inglés
STRUCTURE-BASED DESIGN OF A NOVEL,
POTENT, AND SELECTIVE INHIBITOR FOR
MMP-13 UTILIZING NMR SPECTROSCOPY AND
COMPUTER-AIDED MOLECULAR DESIGN]
JOURNAL OF THE AMERICAN CHEMICAL
SOCIETY, AMERICAN CHEMICAL SOCIETY,
WASHINGTON, DC, US,
Vol 122, 2000, páginas 9648-9654,
XP001010185
ISSN 0002-7863
el documento completo

A WO 97 43239 A (BRITTELLI DAVID R, ZANDT 1-39

560
559

MICHAEL C VAN (US), DIXON BRIAN R (US),

B)

20 de noviembre de 1997 (1997-11-20)

el documento completo

Formulario PCT/ISA/210 (continuación de la segunda página)

(julio de 1992)

página 6 de 6

INFORME DE BUSQUEDA INTERNACIONAL

Solicitud Internacional No PCT/EP 02/01979

Casillero I Observaciones donde se encontró que ciertas**reivindicaciones no eran susceptibles de búsqueda****(Continuación del punto 1 de la primera pagina)**

Este informe de búsqueda no se ha establecido con relación a ciertas reivindicaciones conforme la sección 17(2)(a) por los siguientes motivos

1 [X] Reivindicaciones No

dado que las mismas se refieren a un objeto que no requiere búsqueda por parte de esta Autoridad, a saber

SI BIEN LAS REIVINDICACIONES 35-39 SE REFIEREN A UN MÉTODO DE TRATAMIENTO DEL CUERPO HUMANO/ANIMAL, LA BÚSQUEDA SE LLEVÓ A

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CABO SOBRE LA BASE DE LOS SUPUESTOS EFECTOS DEL
COMPUESTO/COMPOSICIÓN

2 [] Reivindicaciones No

dado que se refieren a partes de la solicitud internacional que no cumplen con los requerimientos prescriptos a tal punto que no se puede realizar una Búsqueda significativa, específicamente

3 [] Reivindicaciones No

dado que son reivindicaciones dependientes y no se encuentran redactadas de acuerdo con los incisos segundo y tercero de la Norma 6 4(a)

**Casillero II Observaciones donde falta unidad de invención
(Continuación del punto 2 de la primera página)**

Esta autoridad de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, tales como

1 [] Dado que el solicitante abonó en término todos los aranceles adicionales, este Informe de Búsqueda Internacional cubre todas las reivindicaciones susceptibles de búsqueda

2 [] Dado la búsqueda de todas las reivindicaciones susceptibles de búsqueda no provocaron un esfuerzo que justifique un arancel adicional, esta Autoridad no invitó al pago de ningún arancel adicional

3 [] Dado que algunos de los aranceles de búsqueda adicionales solicitados fueron abonados en plazo por el solicitante, este Informe de Búsqueda sólo cubre aquellas reivindicaciones por las que se abonó el arancel, específicamente las reivindicaciones No

4 [] El solicitante no abonó los aranceles de búsqueda adicionales en plazo Por lo tanto, este Informe de Búsqueda Internacional se limita a la invención mencionada en primer lugar en las reivindicaciones, la cual se encuentra cubierta por las reivindicaciones No

Observaciones sobre la protesta

[] Los aranceles de búsqueda adicionales se acompañaron a la protesta del solicitante

[] No hubo protesta que acompañe el pago de aranceles de búsqueda adicionales

Formulario PCT/ISA/210 (Continuación de la primera página (1))
(julio de 1998)

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INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de familias de patentes

Solicitud Internacional N° PCT/EP 02/01979

Documento de Patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
SU 119879 A		NINGUNO	
DE 2441959 A	13-03-1975	AU 7296174 A	11-03-1976
		DE 2441959 A1	13-03-1975
		DK 408574 A	05-05-1975
		FR 2243195 A1	04-04-1975
		NL 7411179 A	10-03-1975
		OA 4773 A	31-08-1980
		SE 7410216 A	07-03-1975
		BE 819580 A1	05-03-1975
		JP 50050390 A	06-05-1975
WO 9964400 A	16-12-1999	AU 4429799 A	30-12-1999
		EP 1086085 A1	28-03-2001
		WO 9964400 A1	16-12-1999
		US 2001025044 A1	27-09-2001
WO 9743239 A	20-11-1997	AU 714207 B2	23-12-1999
		AU 3122097 A	05-12-1997

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BR	9709086	A	03-08-1999
CA	2254731	A1	20-11-1997
CN	1225621	A	11-08-1999
EP	0923530	A1	23-06-1999
HR	970244	A1	30-04-1998
JP	11510821	T	21-09-1999
WO	9743239	A1	20-11-1997
ZA	9704030	A	19-02-1998

Formulario PCT/ISA/210 (anexo familia de patentes) (julio de 1992)

PATENT COOPERATION TREATY

RECEIVED ON

02 OCT 2002

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT Patents Fresnes

To:

Hirsch, Denise
PFIZER
Global Research and Development
Fresnes Laboratories
3-9 rue de la Loge, B P 100
F-94265 Fresnes Cedex
FRANCE

WRITTEN OPINION

(PCT Rule 66)

Delai = 30/11/2002.

Date of mailing
(day/month/year)

30/09/2002

Nok' PCT - C+F

Applicant's or agent's file reference
018319 (A476) CD

REPLY DUE

within 2 / 00 months/days
from the above date of mailing

International application No.

PCT/EP 02/01979

International filing date (day/month/year)

11/02/2002

Priority date (day/month/year)

14/02/2001

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

C07D239/96

Applicant

WARNER-LAMBERT COMPANY et al

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

2 This opinion contains indications relating to the following items:

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

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

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

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

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

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

4 The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 14/06/2003

Name and mailing address of the IPEA/

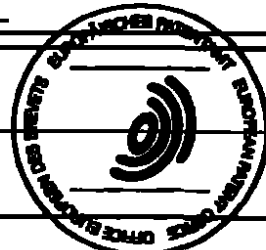


European Patent Office
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Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
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WRITTEN OPINION

International application No. PCT/EP 02/01979

I Basis of the opinion

The basis of this written opinion is the application as originally filed

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT, see also international search report)

V Reasoned statement under Rule 66 2(a)(II) with regard to novelty, inventive step or industrial applicability

- 1 To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out
 - 2 In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)
 - 3 If amendments are filed, the applicant should comply with the requirements of Rule 66 8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out
- NB** Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested

TRATADO DE COOPERACION EN MATERIA DE PATENTES**PCT****OPINION ESCRITA****(Norma PCT 66)****Desde la AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL****A HIRSCH, Dense****Pfizer Global Research and****Development****Fresnes Laboratories****3-9, rue de la Loge, B P 100****F-94265 Fresnes Cedex****Francia****RECIBIDO el 2 de octubre de 2002 Patentes Fresnes****Déla1 30/11/2002****Fecha de correspondencia (día/ mes/ año) 30 de septiembre de
2002 (30-09-2002)****Archivo de referencia del agente o solicitante 018319 (A476) CD**

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Respuesta Dentro de los 2/00 meses/ días desde la fecha de correspondencia

Solicitud Internacional No PCT/EP02/01979

Fecha de presentación internacional (día/ mes/ año) 11 de febrero de 2002 (11/02/2002)

Fecha de Prioridad (día/ mes/ año) 14 de febrero de 2001 (14/02/2001)

Clasificación Internacional de Patentes (IPC) o ambas, clasificación internacional y IPC C07D239/96

Solicitante WARNER- LAMBERT COMPANY et al

- 1 La presente opinión escrita es la primera redactada por la Autoridad Examinadora Preliminar Internacional
- 2 La opinión contiene indicaciones sobre los siguientes puntos

I [X] Bases de la opinión

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- II ☐ Prioridad
- III ☒ Opinión no declarada con respecto a la novedad,
paso inventivo y aplicabilidad industrial
- IV ☐ Falta de unidad de invención
- V ☒ Declaración basada conforme a la Norma 66 2
(a)(11) con respecto a la novedad, el paso inventivo
o la aplicabilidad industrial, citas y explicaciones
que respaldan dicha declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones en la solicitud
internacional

3 Por medio de la presente se invita al solicitante a
responder la opinión

¿Cuándo? Véase el límite de tiempo anteriormente mencionado
El solicitante debe, antes de la fecha de vencimiento de dicho
límite, solicitar a esta Autoridad que se emita una extensión,
véase Norma 66 2(d)

¿Cómo? Para presentar una respuesta escrita, acompañada cuando sea necesario, por reformas, conforme a la Norma 66 3 Para forma e idioma de las reformas, véase Normas 66 8 y 66 9

Además Para oportunidades adicionales de presentación de reformas, véase Norma 66 4

Para la obligación del examinador de presentar las reformas y/o argumentos, véase Norma 66 4bis

Para una comunicación informal con el examinador, véase Norma 66 6

Si no se presenta ninguna respuesta, el informe de examen preliminar internacional será establecido sobre las bases de esta opinión

4 La fecha final por la cual el informe de examen preliminar internacional debe establecerse conforme a la Norma 69 2 es 14/06/2003

Nombre y domicilio para correspondencia de IPEA Oficina de Patente Europea D-80298 Munich Tel (49-89) 2399-0, Tx 523656 epmu d Fax (49-89) 2399-4465

Funcionario Autorizado Examinador de Formalidades (inc
Extensión de límites de tiempo)

Tel (49-89) 2399 2828

Formulario PCT/IPEA/408 (carátula) (marzo de 2002)

OPINIÓN ESCRITA

SOLICITUD INTERNACIONAL No PCT/EP02/01979

I Base de la opinión

La base de la opinión es la solicitud como se presentó originalmente

II Opinión no declarada sobre novedad, paso inventivo y aplicabilidad industrial

La pregunta sobre si la invención reivindicada parece ser novedosa, tener paso inventivo, o ser industrialmente aplicable aun no ha sido ni será objeto del examen preliminar internacional con respecto a las reivindicaciones que no han sido buscadas (Inciso 17(2)(a) y Norma PCT 66 1(e), véase además informe de búsqueda internacional)

V Declaración basada en la Norma 66 2(a)(11) con respecto a la novedad, paso inventivo o aplicabilidad industrial

1 Para que se realice el examen preliminar internacional (véase el punto III anteriormente descrito), se destaca lo siguiente

2 Teniendo en cuenta los documentos citados en el informe de búsqueda internacional, se considera que la invención, como se define en al menos algunas reivindicaciones, que han sido objeto de informe de búsqueda internacional, no parece tener el criterio mencionado en el Inciso PCT 33(1) Es decir, no parece ser novedoso y/o tener paso inventivo (véase informe de búsqueda, en particular documentos citados X y/o Y y referencias de reivindicaciones correspondientes)

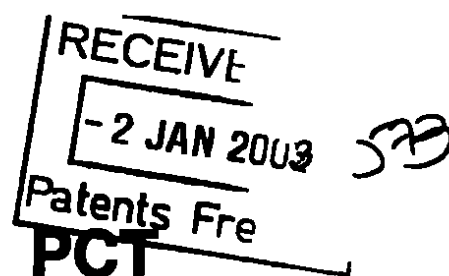
3 Si se presentan reformas, el solicitante debería cumplir con los requisitos de la PCT Norma 66 8 e indicar las bases de las reformas en los documentos de la solicitud como se presentaron originalmente (Inciso PCT 34(2)(b)) de lo contrario las reformas no deben ser consideradas como informe de examen preliminar internacional La atención del

solicitante se redacta en caso de que la solicitud contenga una pluralidad innecesaria de reivindicaciones independientes, ningún examen de cualquier reivindicación puede realizarse

Si el solicitante decide solicitar examen sustantivo detallado, entonces un informe de examen preliminar internacional será establecido normal y directamente. En forma excepcional el examinador puede emitir una segunda opinión escrita, si se lo solicita explícitamente.

Formulario PCT/408AE2 (EPO-03-2002) P20725

PATENT COOPERATION TREATY



From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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 TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year) 23/12/2002	
Applicant's or agent's file reference 018319 (A476) CD	IMPORTANT NOTIFICATION
International application No. PCT/EP 02/ 01979	International filing date (day/month/year) 11/02/2002
Priority date (day/month/year) 14/02/2001	
Applicant WARNER-LAMBERT COMPANY et al	

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

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

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

4. REMINDER

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

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

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

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

Name and mailing address of the IPER/



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Authorized officer

KENNEDY M B
Tel (+49-89) 2399 2828



PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 018319 (A476) CD	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 02/ 01979	International filing date (day/month/year) 11/02/2002	Priority date (day/month/year) 14/02/2001
International Patent Classification (IPC) or national classification and IPC C07D239/96		
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 2 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 consists of a total of _____ 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 supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09/09/2002	Date of completion of this report 18/12/2002
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel (+49-89) 2399-0 Tx 523656 epmu d Fax (+49-89) 2399-4465	Authorized officer BARTHL-WAGNER J C R Tel (+49-89) 2399 2828



Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 02/01979

I Basis of the report

The basis of this international preliminary examination is the application as originally filed

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66 1(e) PCT), see also international search report)

V Reasoned statement under Rule 66 2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references)

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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

[Se observa un sello que reza] Recibido 2 de enero de 2003

Patentes [Sigue un texto ilegible]

PCT**NOTIFICACIÓN DE LA TRANSMISIÓN DEL INFORME DE EXAMEN
PRELIMINAR INTERNACIONAL**

(PCT Norma 71 1)

De la AUTORIDAD DE EXAMEN PRELIMINAR INTERNACIONAL

Para Hirsch, Dense

PFIZER

Investigación y Desarrollo Global

Fresnes Laboratories

3-9 rue de la Loge, B P 100,

F-94265 Fresnes Cedex

FRANCIA

Fecha de envío (día/mes/año) 23/12/2002

Referencia del archivo del solicitante o del apoderado 018319

(A476) CD

NOTIFICACION IMPORTANTE

Solicitud Internacional N° PCT/EP 02/01979

Fecha de solicitud internacional (día/mes/año) 11/02/2002

Fecha de prioridad (día/mes/año) 14/02/2001

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Solicitante WARNER-LAMBERT COMPANY et al

1 Por la presente se notifica al solicitante que la Autoridad de Examen Preliminar Internacional transmite adjunto el informe de examen preliminar internacional y sus anexos, si los tiene, establecidos en la solicitud internacional

2 Se enviará una copia del informe y sus anexos, si los tiene, a la Oficina Internacional para que se comuniquen a todas las Oficinas seleccionadas

3 Cuando cualquiera de las Oficinas seleccionadas lo requiera, la Oficina Internacional preparará una traducción al inglés del informe (pero no de los anexos) y transmitirá dicha traducción a esas Oficinas

4 RECORDATORIO

El solicitante deberá ingresar en la fase nacional ante cada una de las Oficinas seleccionadas a través de la realización de ciertos actos (presentar traducciones y abonar las tasas nacionales) dentro de los 30 meses a partir de la fecha de prioridad (o más tarde en algunas Oficinas) (Artículo 39 (1)) (ver también el recordatorio enviado por la Oficina Internacional con el Formulario PCT/IB/301)

S70

S78

Cuando se debe presentar una traducción en una Oficina seleccionada, esa traducción debe contener una traducción de cualquier anexo del informe de examen preliminar internacional. Es responsabilidad del solicitante preparar y presentar dicha traducción directamente en cada una de las Oficinas involucradas.

Para mayores detalles acerca de los plazos y requisitos correspondientes a cada Oficina seleccionada, ver el Volumen II de la Guía del Solicitante de PCT.

Se recuerda al solicitante el Artículo 33(5), que contempla que los criterios de novedad, actividad inventiva y aplicación industrial descritos en el Artículo 33(2) a 33(4) solamente sirven para el examen preliminar internacional y que "cualquier Estado Suscrito puede aplicar criterios adicionales o diferentes a efectos de decidir si, en ese Estado, las invenciones reivindicadas son patentables o no" (ver también Artículo 27(5)). Por ejemplo, dichos criterios adicionales se pueden relacionar con las exenciones de patentabilidad, requisitos para posibilitar la revelación, claridad y respaldo de las reivindicaciones.

Nombre y dirección de la IPEA

579

Oficina de Patentes Europea

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Funcionario Autorizado KENNEDY M B

[Aparece un sello en otro idioma]

Teléfono No (+49-89) 2399 2828

Formulario PCT/IPEA/416 (Agosto de 2002) P20473

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES**PCT****INFORME DE EXAMEN PRELIMINAR INTERNACIONAL****(PCT Artículo 36 y Norma 70)**

**(Informe racionalizado de acuerdo a la Notificación del
Presidente de la EPO publicada en el OJ11/2001)**

**Referencia del archivo del solicitante o del apoderado 018319
(A476) CD**

**PARA MAS ACCIONES Ver la Notificación de la Transmisión del
Informe de Examen Preliminar Internacional (Formulario
PCT/IPEA/416)**

Solicitud Internacional N° PCT/EP 02/01979

Fecha de solicitud internacional (día/mes/año) 11/02/2002

Fecha de Prioridad (día/mes/año) 14/02/2001

**Clasificación de Patente Internacional (IPC) o clasificación
nacional e IPC**

C07D239/96

Solicitante WARNER-LAMBERT COMPANY et al

**1 Este informe de examen preliminar internacional ha sido
preparado por la Autoridad de Examen Preliminar Internacional
y se transmite al solicitante conforme al Artículo 36**

2 Este **INFORME** consiste de un total de 2 hojas, incluyendo la cubierta

☐ También se acompañan los **ANEXOS** de este informe, es decir, las hojas descripción, las reivindicaciones y/o los dibujos que han sido modificados y son la base de este informe y/o las hojas que contienen las rectificaciones realizadas ante esta Autoridad (ver Norma 70 16 y Sección 607 de las Instrucciones Administrativas bajo el PCT)
Estos anexos consisten de un total de [blanco] hojas

3 Este informe contiene las indicaciones relacionadas con los siguientes items

- I ☒ Base del informe
- II ☐ Prioridad
- III ☒ No se establece una opinión con respecto a la novedad, la actividad inventiva y la aplicación industrial
- IV ☐ Falta de unidad en la invención
- V ☒ Declaración razonada bajo el Artículo 35(2) con respecto a la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones que apoyan dicha declaración
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la Solicitud Internacional

VIII ☐ Ciertas observaciones acerca de la Solicitud Internacional

Fecha de presentación de la demanda 09/09/2002

Fecha de finalización de este informe 18/12/2002

Nombre y dirección de la IPEA/

Oficina de Patentes Europea

D-80298 Munich

Teléfono No (+49-89) 2399-0, Tx 523656 epmu d

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Funcionario Autorizado BARTHL-WAGNER J C R

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Formulario PCT/IPEA/409 (cubierta) P20476 (octubre de 2002)

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No PCT/EP 02/01979

I Base del Informe

La base de este examen preliminar internacional es la solicitud según se presentó originalmente

III No se establece opinión con respecto a la novedad, actividad inventiva y aplicación industrial

No se ha planteado, con respecto a las reivindicaciones que no se buscaron, si la invención reivindicada parece ser novedosa, involucrar actividad inventiva o ser aplicable industrialmente en el examen preliminar internacional (Artículo 17 (2) (a) o (3) y la Norma 66 1 (e) del PCT), ver también el informe de búsqueda internacional)

V Declaración razonada bajo la Norma 66 2 (a) (ii) con respecto a la novedad, la actividad inventiva y la aplicación industrial

En la medida que se efectuó el examen preliminar internacional (ver punto III anterior), se señala lo siguiente

En vista de los documentos citados en el informe de búsqueda internacional, se considera que la invención -según fue definida por lo menos en algunas de las reivindicaciones, que fueron el objeto del informe de búsqueda internacional- no parece satisfacer el criterio mencionado en el Artículo 33(1) PCT, es decir que no parece ser novedosa y/o involucrar actividad inventiva (ver informe de búsqueda internacional, en particular los documentos citados X y/o Y y las referencias de las reivindicaciones correspondientes)

Formulario PCT/409NE2 (EPO-03-2002) P20758

PATENT COOPERATION TREATY

RECEIVED ON

19 MAY 2003

Patents Fresnes

PCT

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)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 018319 (A476) CD	
International application No. PCT/EP02/01979	International filing date (day/month/year) 11 February 2002 (11 02 02)

1 The following indications appeared on record concerning

☒ 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 ☒ 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

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ 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 8238
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586

PCT/EP02/01979

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

[Se observa un sello que reza] Recibido el 19 de mayo de
2003 Patentes Fresnes

PCT**NOTIFICACIÓN DE LA INSCRIPCIÓN DE UN CAMBIO**

(PCT Norma 92bis 1 e Instrucciones Administrativas, Sección
422)

De la OFICINA INTERNACIONAL

Para Hirsch, Dense

Pfizer

Investigación y Desarrollo Global

Fresnes Laboratories

3-9 rue de la Loge, B P 100

F-94265 Fresnes Cedex

FRANCIA

Fecha de envío (día/mes/año) 25 de abril de 2003 (25/04/03)

Referencia del archivo del solicitante o del apoderado 018319

(A476) CD

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional N° PCT/EP 02/01979

Fecha de solicitud internacional (dia/mes/año) 11 de febrero
de 2002 (11/02/02)

1 La siguiente información se encontraba inscrita con
respecto a

- ☒ el solicitante
- ☐ el inventor
- ☐ el agente
- ☐ el representante

Nombre y domicilio

WARNER-LAMBERT COMPANY

201 Tabor Road

Morris Plains, NJ 07950

Estados Unidos de América

Nacionalidad Estadounidense (US)

Estado de Residencia Estados Unidos de América (US)

Teléfono No [Blanco]

Fax No [Blanco]

Teleimpresora No [Blanco]

2 La Oficina Internacional notifica por la presente al
solicitante que se ha inscripto el siguiente cambio con
respecto a

388 54A

- ☐ la persona
- ☒ el nombre
- ☐ el domicilio
- ☐ la nacionalidad
- ☐ la residencia

Nombre y domicilio**WARNER-LAMBERT COMPANY LLC****201 Tabor Road****Morris Plains, NJ 07950****Estados Unidos de América****Nacionalidad Estadounidense (US)****Estado de Residencia Estados Unidos de América (US)****Teléfono No [Blanco]****Fax No [Blanco]****Teleimpresora No [Blanco]****3 Observaciones adicionales, si fueran necesarias [Blanco]****4 Una copia de esta notificación se ha enviado a**

- ☒ la Oficina Receptora
- ☐ la Autoridad de Búsqueda Internacional
- ☒ la Autoridad de Examen Preliminar Internacional
- ☐ las Oficinas designadas correspondientes

- ☒ las Oficinas seleccionadas correspondientes
☐ otra

Oficina Internacional de la WIPO

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1211 Ginebra 20, Suiza

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Formulario PCT/IB/306 (Marzo 1994)

005603770

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064572 A1

(51) International Patent Classification⁷ C07D 239/96
401/12 405/12 409/12, 405/14 409/14 471/04 403/12,
403/10, 410/10, 413/10 401/06, A61K 31/5025 31/505

(21) International Application Number^{*} PCT/EP02/01979

(22) International Filing Date^{*} 11 February 2002 (11.02.2002)

(25) Filing Language English

(26) Publication Language English

(30) Priority Data
60/268 661 14 February 2001 (14.02.2001) US

(71) Applicant (for all designated States except US)
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and Development Fresnes Laboratories, 3-9, rue de la
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(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)

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations 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,

[Continued on next page]

WO 02/064572 A1

(54) Title QUINAZOLINES AS MMP 13 INHIBITORS

(57) Abstract A compound selected from those of formula (I) in which R₁ represents a group selected from hydrogen, amino, alkyl, alkenyl, aralkyl, aryl, aralkyl, heterocycle and cycloalkylalkyl, optionally substituted, W represents oxygen, sulphur or =N, R in which R is as defined in the description, X₁, X₂ and X₃ represent nitrogen or -C(R₄) in which R₄ is as defined in the description, Y represents oxygen, sulphur, NH or N(C₁-C₆)alkyl, Z represents oxygen, sulphur, -NR₇ in which R₇ is as defined in the description, and optionally carbon atom, n is an integer from 1 to 8 inclusive, Z₁ represents -CR₈R₉, wherein R₈ and R₉ are as defined in the description, A represents aromatic or non-aromatic, heterocyclic or non-heterocyclic ring system, m is an integer from 0 to 7 inclusive, the group(s)-R₂ is (are) is as defined in the description, R₃ represents hydrogen, alkyl, alkenyl, alkynyl, or a group of formula in which Z₂, B, R₅, P and Q are as defined in the description, optionally the racemic forms thereof, isomers thereof, N-oxides thereof and the pharmaceutically acceptable salts thereof and medicinal products containing the same are useful as specific inhibitors of type 13 matrix metalloproteinase.

WO 02/064572 A1



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.

QUINAZOLINES AS MMP-13 INHIBITORS

Field of the invention.

The present invention relates to novel substituted quinazolines which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

Technological background of the invention.

Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating pathologies associated with the destruction of the extracellular matrix and with cancer

The invention relates to a substituted quinazoline of formula (I)



R_1 represents a group selected from

- hydrogen, amino,
- (C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)alkynyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, aryl, aryl(C₁-C₆)alkyl, heterocycle, and 3- to 6-membered cycloalkyl(C₁-C₆)alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, (C₁-C₆)alkyl, cyano, halo(C₁-C₆)alkyl, C(=O)OR₄, OR₄ and SR₄, in which R₄ represents hydrogen or (C₁-C₆)alkyl.

W represents an oxygen atom, a sulphur atom, or a group $=N-R'$, in which R' represents (C_1-C_6) alkyl, hydroxyl, or cyano,

X_1 , X_2 and X_3 represent, independently of each other, a nitrogen atom or a group $-C-R_6$ in which R_6 represents a group selected from hydrogen, (C_1-C_6) alkyl, ammo, mono(C_1-C_6)alkylammo, di(C_1-C_6)alkylammo, hydroxyl, (C_1-C_6) alkoxy, and halogen, with the proviso that not more than two of the groups X_1 , X_2 and X_3 simultaneously represent a nitrogen atom,

Y represents a group selected from oxygen atom, sulphur atom, $-NH$, and $-N(C_1-C_6)$ alkyl,

Z represents

- an oxygen atom, a sulphur atom,
- or a group $-NR_7$ in which R_7 represents a group selected from hydrogen, (C_1-C_6) alkyl, aryl(C_1-C_6)alkyl, cycloalkyl, aryl, and heteroaryl, and
- when Y is an oxygen atom, a sulphur atom, or a group $-N(C_1-C_6)$ alkyl, Z optionally represents a carbon atom which is unsubstituted or substituted with a (C_1-C_6) alkyl, an aryl, an aryl(C_1-C_6)alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9 , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, halo(C_1-C_6)alkyl, halogen, amino, OR_4 , SR_4 or $C(=O)OR_4$ in which R_4 represents a hydrogen or (C_1-C_6) alkyl, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,

• and when one of the carbon atoms in the hydrocarbon chain Z_1 is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group $-C(=Y)-Z-$ optionally may be absent in the general formula (I),

A represents a group selected from

- 5 • aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

10 m is an integer from 0 to 7 inclusive,

the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, NO_2 , SCF_3 , $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_3(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_3(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

15 • X_3 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or (C_1-C_6) alkyl,

 • k is an integer from 0 to 3 inclusive,

 • R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,

20 • X_4 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C_1-C_6) alkyl group,

 • R_{12} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which

may be identical or different, selected from (C₁-C₆)alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

R₃ represents a group selected from.

- 5 • hydrogen,
- (C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo(C₁-C₆)alkyl, cycloalkyl, -C(=O)NR₁₀R₁₁, -C(=O)OR₁₀, OR₁₀, and SR₁₀, in which R₁₀ and R₁₁, which may be identical or different, represent hydrogen or (C₁-C₆)alkyl,
- 10 • and the group of formula



✓ in which p is an integer from 0 to 8 inclusive,

- ✓ Z₂ represents -CR₁₃R₁₄ wherem R₁₃ and R₁₄, independently of each other, represent a group selected from hydrogen, (C₁-C₆)alkyl, phenyl, halo(C₁-C₆)alkyl, halogen, amino, OR₄, SR₄ and -C(=O)OR₄ in which R₄ represents hydrogen or (C₁-C₆)alkyl, and
- 15 • when p is greater than or equal to 2, the hydrocarbon chain Z₂ optionally contains one or more multiple bonds,
- and/or one of the carbon atoms in the hydrocarbon chain Z₂ may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C₁-C₆)alkyl, or a carbonyl group,
- 20 • B represents a group selected from.
- an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
- 25

- a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

✓ q is an integer from 0 to 7 inclusive,

- 5 ✓ the group(s) R_5 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{18}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, $-R_{19}-C(=O)OR_{15}$, $-X_6-R_{20}$, and $-C(=O)-R_{21}-NR_{15}R_{16}$ in which
- 10 - X_7 represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a (C_1-C_6) alkyl group,
- 15 - k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- 20 - R_{18} represents a group selected from (C_1-C_6) alkyl, $-R_{21}-NR_{15}R_{16}$, $-R_{21}-NR_{15}-C(=O)-R_{21}-NR_{16}R_{17}$, and $-C(=O)O-R_{21}-NR_{15}R_{16}$ in which R_{21} represents a linear or branched (C_1-C_6) alkylene group, and R_{15} , R_{16} and R_{17} are as defined hereinbefore,

- R_{19} represents a (C_3-C_6) cycloalkyl group,
- X_6 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C_1-C_6) alkyl group,

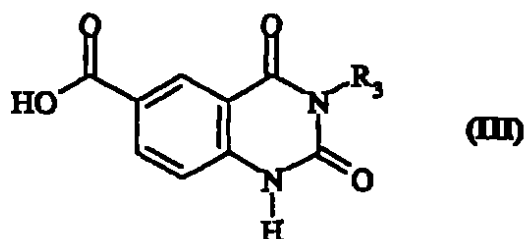
- 5 - R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and $-C(=O)OR_4$ wherein R_4 represents hydrogen or (C_1-C_6) alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4
- 10 heteroatoms selected from nitrogen, oxygen and sulphur,

with the proviso that when X_1 represents a nitrogen atom, X_2 cannot represent a carbon atom substituted with a methyl group or with $NH-CH_3$,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof

- 15 The compounds of the present invention are useful as inhibitors, in particular as selective inhibitors, of the enzyme matrix metalloprotease-13 (MMP-13)

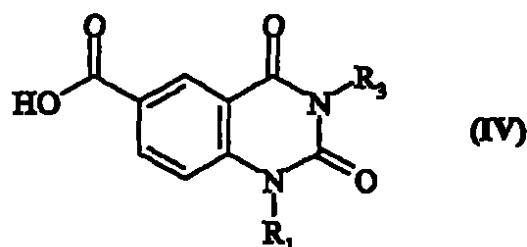
The invention also relates to compounds used mainly as intermediates for the synthesis of the compounds of formula (I). These intermediate compounds have the general formula (III) below



20

in which R_3 has the same meaning as defined for the compound of formula (I)

The invention also relates to compounds used mainly as intermediates for the synthesis of the compound of formula (I), which have the general formula (IV) below

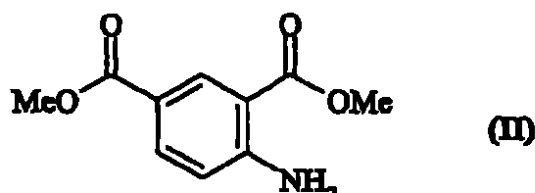


in which R_1 et R_3 have the same meaning as for a compound of formula (I)

5 The invention also relates to a process for manufacturing the compound of formula (I) in which.

- R_2 , R_3 , Z_1 , A , n and m are as defined in the compound of general formula (I),
- X_1 , X_2 , X_3 are each a group $-C-R_6$ in which R_6 represents a hydrogen atom,
- Y is O,
- 10 - Z is $-N-R_7$ in which R_7 is as defined in the compound of general formula (I),
- and W is O

This process is characterized in that it comprises the reaction of a compound of formula (II)



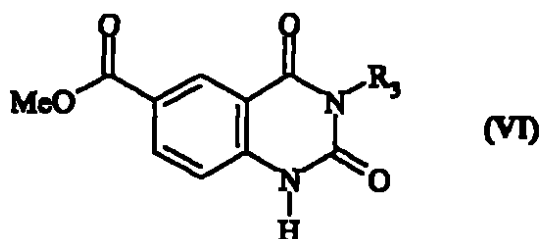
15 with pyridine and the compound of general formula (V)



in which R_3 is as defined above for the compound of formula (I),
to give the compound of general formula (VI)

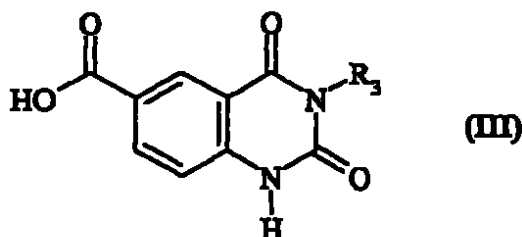
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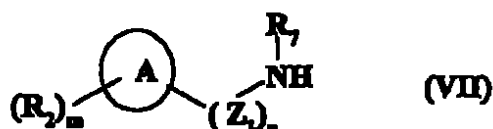
in which R₃ is as defined herembefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which R₃ is as defined above



5

In a subsequent step of the synthetic process, the compound of general formula (III) obtained above is reacted, in the presence of an acid activator such as O-[(ethoxycarbonyl)cyanomethylenamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) with the compound of general formula (VII)



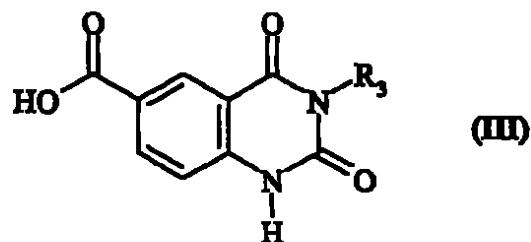
10

in which R₇ is selected from hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, cycloalkyl, aryl and heteroaryl, and A, R₂, Z₁, n and m are as defined above for the compound of formula (I), to give the compound of general formula (I) in which R₁ represents hydrogen, X₁, X₂ and X₃ are each -C-R₆ in which R₆ represents hydrogen atom, Y is O, Z is N-R₇, W is O, , and A, R₂, Z₁, n and m are as defined hereinbefore.

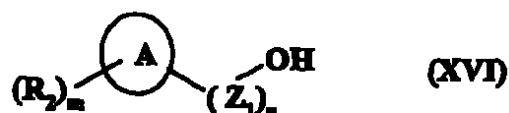
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In particular, when W is O, Y is O and Z is O, the compounds of formula (I) corresponding to this definition may be obtained by reacting a compound of general formula (III)

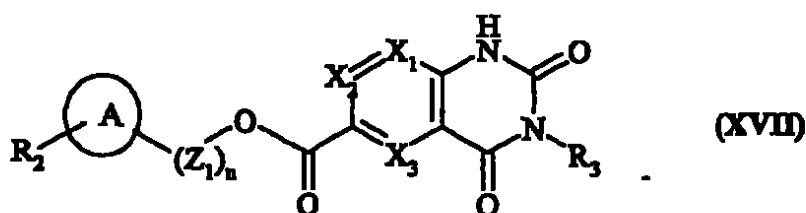
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in which R_3 is as defined in the compound of general formula (I),
with a compound of general formula (XVI)



5 in which Z_1 , A , R_2 , n and m are as defined in the compound of general formula (I),
to give a compound of general formula (XVII)



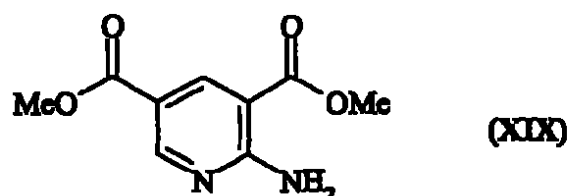
in which A , R_2 , R_3 , Z_1 , m and n are as defined for the compound of general formula (I), and
 X_1 , X_2 , and X_3 are each $-C-R_6$ in which R_6 represents hydrogen atom,

10 followed by reacting the compound of formula (XVII), in presence of a base, with the
compound of general formula (VIII), $X-R_1$, in which R_1 is as defined for the compound of
formula (I) and X is a leaving group such as halogen,
to give the compound of general formula (I) in which X_1 , X_2 and X_3 are each $-C-R_6$ in
which R_6 is as defined hereinbefore, W is O, Y is O, Z is O, and R_1 , R_2 , R_3 , Z_1 , A , n and m
15 are as defined hereinbefore.

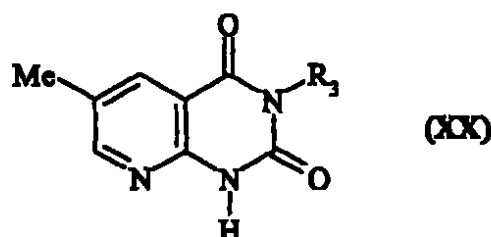
In particular, when X_2 and X_3 are each $-C-R_6$ in which R_6 represents hydrogen atom, X_1 is
N, Z is O and Y is O, the compounds of formula (I) corresponding to this definition may be
obtained by reacting a compound of general formula (XIX)

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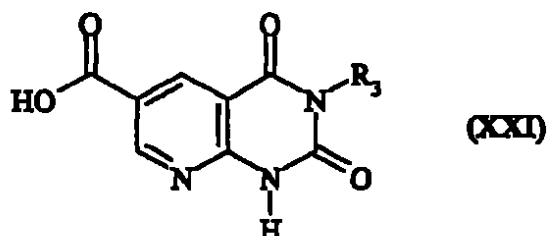


with pyridine and a compound of general formula $O=C=N-R_3$ (V) in which R_3 is as defined in the compound of formula (I),
to give a compound of general formula (XX)



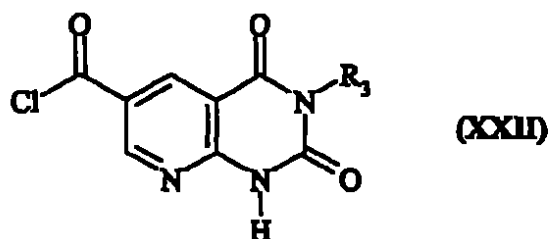
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in which R_3 is as defined hereinbefore,
followed by reacting the compound of general formula (XX) in the presence of $KMnO_4$ to give the compound of general formula (XXI)



10

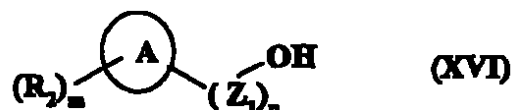
in which R_3 is as defined hereinbefore,
followed by reacting a compound of general formula (XXI) in the presence of $SOCl_2$ and $CHCl_3$ to give the compound of general formula (XXII)



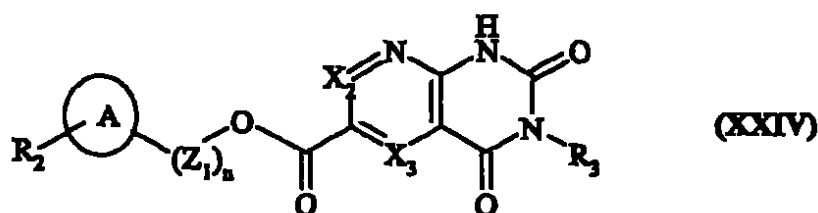
in which R_3 is as defined hereinbefore,

15

followed by reacting the compound of formula (XXII) with the compound of general formula (XVI)



in which A, R₂, Z₁, n and m are as defined in the compound of formula (I),
to give the compound of general formula (I)



5 in which A, R₂, R₃, Z₁, m and n are as defined hereinbefore, X₂ and X₃ are each -C-R₆ in which R₆ is as defined hereinbefore, and R₃ are as defined for the compound of general formula (I)

The invention also relates to a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable excipient.

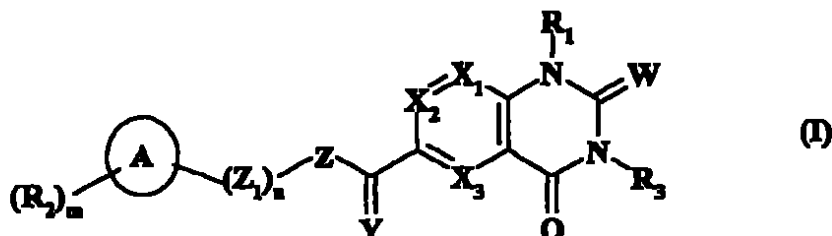
10 The invention also relates to the use of a compound of formula (I) for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease (MMP-13)

15 The invention also relates to a method for treating a disease or complaint involving a therapy by inhibition of matrix metalloprotease, and more particularly MMP-13, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient.

Detailed description of the invention

20 The Applicant has identified according to the invention novel compounds that are matrix metalloprotease inhibitors, and more specifically novel compounds that are MMP-13 inhibitors

One subject of the invention is thus a substituted quinoxaline of formula (I)



in which R_1 , R_2 , R_3 , X_1 , X_2 , X_3 , W , Y , Z , Z_1 , n and m are as defined hereinbefore in the compound of general formula (I),

5 optionally the racemic forms thereof, isomers forms thereof, N-oxides thereof, and the pharmaceutically acceptable salts thereof.

The invention relates particularly to the compounds of general formula (I) in which

- R_1 represents hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl or 3- to 6-membered cycloalkyl (C_1-C_6) alkyl,

- 10 • W represents an oxygen atom or a sulphur atom,
- X_1 represents a nitrogen atom or $-C-R_6$ in which R_6 represents a hydrogen atom,
- X_2 and X_3 represent each $-C-R_6$ in which R_6 represents a hydrogen atom,
- Y represents an oxygen atom,
- Z represents an oxygen atom or $-NR_7$ in which R_7 represents a hydrogen atom

15 The invention also relates to the compounds of general formula (I) in which

- n is an integer from 1 to 6 inclusive,

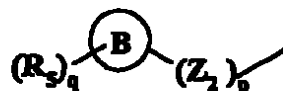
- Z_1 represents $-CR_8R_9$ wherein R_8 represents a hydrogen atom and R_9 represents a hydrogen atom or a methyl group, and

- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains a double bond,

- 20 - or, one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, or a sulphur atom which is unsubstituted or substituted with one or two oxygens,

- A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, piperidyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,
 - m is an integer from 0 to 7 inclusive,
- 5 • the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which
- ✓ X_5 represents O, S or NH,
- 10 ✓ k is an integer from 0 to 3 inclusive,
- ✓ R_{10} and R_{11} , identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
 - ✓ X_4 represents $-CH_2-$, or an oxygen atom,
 - ✓ R_{12} represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen,
- 15 hydroxyl and amino

The invention also relates to the compounds of general formula (I) in which R_3 represents hydrogen, (C_1-C_6) alkyl or the group of formula



- ✓ in which p is an integer from 0 to 3 inclusive,
- 20 ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, methyl, or phenyl, and
- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,

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- or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl, or a carbonyl group,
- 5 ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- ✓ q is an integer from 0 to 3 inclusive,
- 10 ✓ the group(s) R_3 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$ in which
- 15 • X_7 is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- 20 The invention relates more particularly to the compounds of general formula (I) in which R_1 represents a group selected from
- hydrogen, amino,
 - (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, mono (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, aryl, aryl (C_1-C_6) alkyl, heterocycle, and 3- to
- 25 6-membered cycloalkyl (C_1-C_6) alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, $(C_1-$

C₆)alkyl, cyano, halo(C₁-C₆)alkyl, C(=O)OR₄, OR₄ and SR₄, in which R₄ represents hydrogen or (C₁-C₆)alkyl,

W represents an oxygen atom, a sulphur atom, or a group =N-R', in which R' represents (C₁-C₆)alkyl, hydroxyl, or cyano,

- 5 X₁ represents a nitrogen atom or a group -C-R₆ in which R₆ represents hydrogen atom, X₂ and X₃ represent, independently of each other, a group -C-R₆ in which R₆ represents a group selected from hydrogen, (C₁-C₆)alkyl, amino, hydroxyl and halogen,

Y represents an oxygen atom,

- 10 Z represents an oxygen atom, or a group -NR₇ in which R₇ represents a group selected from hydrogen, and (C₁-C₆)alkyl,

n is an integer from 1 to 6 inclusive,

Z₁ represents -CR₈R₉ wherein R₈ and R₉, independently of each other, represent a group selected from hydrogen, (C₁-C₆)alkyl and hydroxyl, and

- 15
 - when n is greater than or equal to 2, the hydrocarbon chain Z₁ optionally contains one or more multiple bonds,
 - or one of the carbon atoms in the hydrocarbon chain Z₁ may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C₁-C₆)alkyl,

- 20 A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxanyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

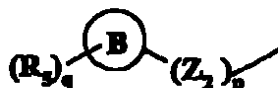
m is an integer from 0 to 3 inclusive,

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the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_3(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_3(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

- 5 • X_3 represents O, S or NH,
 • k is an integer from 0 to 3 inclusive,
 • R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
 • X_4 represents $-CH_2-$, or an oxygen atom,
 10 • R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, and hydroxyl,

R_3 represents a group selected from hydrogen, (C_1-C_6) alkyl, and the group of formula



- ✓ in which p is an integer from 0 to 6 inclusive,
 15 ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, and hydroxy, and
 • when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
 • or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an
 20 oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,
 ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
 25 ✓ q is an integer from 0 to 3 inclusive,

✓ the group(s) R_5 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_6-R_{20}$ in which

- X_7 is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur

20 The invention also relates to the compounds of general formula (I) in which.

R_1 represents a group selected from hydrogen, mono (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, aryl, aryl (C_1-C_6) alkyl, and 3- to 6-membered cycloalkyl (C_1-C_6) alkyl,

W represents an oxygen atom, or a sulphur atom,

25 X_1 represents a nitrogen atom or a $-CH$ group,

X_2 and X_3 represent a $-CH$ group,

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Y represents a group selected from oxygen atom, sulphur atom, -NH, and -N(C₁-C₆)alkyl,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

5 Z₁ represents -CR₈R₉ wherein R₈ and R₉, independently of each other, represent a group selected from hydrogen, (C₁-C₆)alkyl and hydroxy, and

- when n is greater than or equal to 2, the hydrocarbon chain Z₁ optionally contains one double bond,
 - or one of the carbon atoms in the hydrocarbon chain Z₁ may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a -NH group,
- 10

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

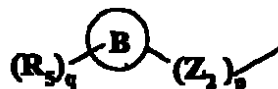
m is an integer from 0 to 3 inclusive,

15 the group(s) R₂, which may be identical or different, is (are) selected from (C₁-C₆)alkyl, halogen, -CN, -CF₃, -OCF₃, -NR₁₀R₁₁, -OR₁₀, -SR₁₀, -SO₂R₁₀, -(CH₂)_kSO₂NR₁₀R₁₁, -X₃(CH₂)_kC(=O)OR₁₀, -(CH₂)_kC(=O)OR₁₀, -X₃(CH₂)_kC(=O)NR₁₀R₁₁, -(CH₂)_kC(=O)NR₁₀R₁₁, and -X₄-R₁₂ in which

- X₃ represents O, S or NH,
 - k is an integer from 0 to 3 inclusive,
 - R₁₀ and R₁₁, which may be identical or different, are selected from hydrogen and (C₁-C₆)alkyl,
 - X₄ represents -CH₂-, or an oxygen atom,
- 20

• R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, and hydroxyl,

R_3 represents a group selected from methyl and the group of formula



- 5 ✓ in which p is an integer from 0 to 3 inclusive,
- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, and hydroxy, and
- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,
- 10 • or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,
- ✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- 15 ✓ q is an integer from 0 to 3 inclusive,
- ✓ the group(s) R_s , which may be identical or different, is (are) selected from
- 20 (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_8-R_{20}$ in which
- X_7 is S, O or NH,
- 25 • k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,

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- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- 5 • R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur

- 10 The invention also relates to the compounds of general formula (I) in which.
 R_1 represents hydrogen, (C_1-C_6) alkyl, (C_3-C_6) alkenyl, aryl (C_1-C_6) alkyl, 3- to 6-membered cycloalkyl (C_1-C_6) alkyl,

W represents an oxygen atom,

X^1 represents $-CH$ group or nitrogen atom, and X^2 and X^3 represent each $-CH$ group,

- 15 Y represents an oxygen atom,

Z represents an oxygen atom or a $-NH$ group,

n is an integer from 1 to 3 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9 , independently of each other, represent a group selected from hydrogen and methyl, and

- 20 • when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a $-NH$ group,

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

m is an integer from 0 to 3 inclusive,

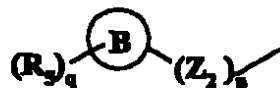
the group(s) R₂, which may be identical or different, is (are) selected from (C₁-C₆)alkyl, halogen, -CN, -CF₃, -OCF₃, -NR₁₀R₁₁, -OR₁₀, -SR₁₀, -SO₂R₁₀, -(CH₂)_kSO₂NR₁₀R₁₁, -X₃(CH₂)_kC(=O)OR₁₀, -(CH₂)_kC(=O)OR₁₀, -X₃(CH₂)_kC(=O)NR₁₀R₁₁, and -(CH₂)_kC(=O)NR₁₀R₁₁, in which.

- X₃ represents O, S or NH,

- k is an integer from 0 to 3 inclusive,

- R₁₀ and R₁₁, which may be identical or different, are selected from hydrogen and (C₁-C₆)alkyl,

R₃ represents the group of formula



✓ in which p is an integer from 0 to 3 inclusive,

✓ Z₂ represents -CR₁₃R₁₄ wherein R₁₃ and R₁₄, independently of each other, represent a group selected from hydrogen, and methyl, and

- when p is greater than or equal to 2, the hydrocarbon chain Z₂ optionally contains one double bond,

- or one of the carbon atoms in the hydrocarbon chain Z₂ may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C₁-C₆)alkyl,

✓ B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

✓ q is an integer from 0 to 3 inclusive,

- ✓ the group(s) R_5 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2N(R_{15})-(CH_2)_{k2}NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$, in which
- X_7 is S, O or NH,
 - k is an integer from 0 to 3 inclusive,
 - $k1$ is an integer from 0 to 2 inclusive,
 - $k2$ is an integer from 1 to 4 inclusive,
 - R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl

The invention also relates to the compounds of general formula (I) in which R_1 represents a hydrogen atom or a (C_1-C_6) alkyl group

- 15 The invention also relates to the compounds of general formula (I) in which W represents an oxygen atom, Y represents an oxygen atom, Z represents a NH group, Z_1 represents a methylene group, and n is equal to one.

The invention also relates to the compounds of general formula (I) in which X_1 represents a $-CH$ group or a nitrogen atom, and X_2 and X_3 represent each a $-CH$ group

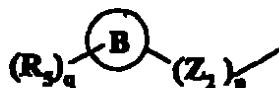
- 20 The invention also relates to the compounds of general formula (I) in which X_1 and X_3 represent each a $-CH$ group, and X_2 represents a $-CH$ group or a nitrogen atom.

The invention also relates to the compounds of general formula (I) in which X_1 and X_3 represent each a $-CH$ group, and X_2 represents a nitrogen atom.

- 25 The invention also relates to the compounds of general formula (I) in which A represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl and benzofurazanyl, m is equal to

0 or 1, and R_2 represents a group selected from (C_1-C_6) alkoxy, hydroxy, halogen, and (C_1-C_6) thioalkoxy

The invention also relates to the compounds of general formula (I) in which R_3 represents a group of formula



in which

p is equal to one,

Z_2 represents a methylen group,

10 B represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

q is an integer from 0 and 2 inclusive,

and R_2 represents a group selected from halogen, CN, $-(CH_2)_kNR_{15}R_{16}$, $-S(O)_{k1}R_{15}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-(CH_2)_kC(=O)OR_{15}$, $-X_6-R_{20}$ and $-(CH_2)_kC(=O)NR_{15}R_{16}$, in which

k is an integer from 0 to 1 inclusive,

15 $k1$ is an integer from 0 to 2 inclusive,

R_{15} and R_{16} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,

X_6 represents a single bond,

20 R_{20} represents a 5-membered heterocyclic ring comprising from 3 to 4 heteroatoms selected from oxygen and nitrogen and optionally substituted by a methyl group or an oxo group

Among the groups defined above, the following substituents are particularly preferred

- halogen F, Cl, Br, I, preferably F, Br and Cl,

25 - (C_1-C_6) alkyl linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,

- (C_1-C_6) alkoxy linear or branched containing from 1 to 6 and preferably from 1 to 3 carbon atoms,

- (C₃-C₆)alkenyl containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly allyl,
- (C₃-C₆)alkynyl containing from 3 to 6 and preferably 3 or 4 carbon atoms, more particularly propargyl,
- 5 - aryl containing from 5 to 10 and preferably 5 or 6 carbon atoms,
- heteroaryl aryl group interrupted with one or several hetero atom selected from nitrogen, oxygen and sulphur. The term "interrupted" means that the hetero atom can replace a carbon atom of the ring. Examples of such groups containing a heteroatom are, inter alia, thienyl, pyridyl, benzofurazanyl,
- 10 - heterocycle an aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur
- aryl(C₁-C₆)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 4 carbon atoms,
- cycloalkyl containing from 3 to 8 and preferably from 3 to 6 carbon atoms,
- 15 - cycloalkyl(C₁-C₆)alkyl in which the alkyl contains from 1 to 6 and preferably from 1 to 3 carbon atoms and the cycloalkyl contains from 3 to 6 carbon atoms
- multiple bond represent a double bond or a triple bond

Among the compounds of the present invention that are preferred are the compounds described below in Examples 1 to Example 227

- 20 More particularly, the preferred compounds of the present invention are compound of formula (I) which are
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-
 - 25 carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide
 - 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
 - 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt
- Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate
- 5 - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 10 - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid
- 15 - 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 20 - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate
- 25 - 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 30 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid

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- 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid
- 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 5 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-
- 10 tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-3-[4-(2-methyl-2H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide
- 15 - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide
- Benzo[1,3]dioxol-5-ylmethyl-3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 20 (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 25 - 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 30 (benzo[1,3]dioxol-5-ylmethyl)amide
- 1-Methyl-3-[4-(1-methyl-1H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- 4-Pyridymethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 5 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 10 - 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 15 - 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 20 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 25 - 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid
- 30 - 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamide

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- 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 5 - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid
- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid
- 10 - Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
- 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- 15 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide
- 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate
- 20 - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid
- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetic acid
- 25 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide
- Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetate
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide
- 30 - 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide
- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyrimidin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinoxalin-3-ylmethyl}-benzoate
- 5 - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid
- 10 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid hemimagnesium salt
- Example 164 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid
- 15 - 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide
- Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoate
- 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide
- 20 - and 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in J Pharm Sci., 1977, vol 66 1-19. However, the expression "pharmacologically acceptable salts of a compound of formula (I) with a basic function" means the addition salts of the compounds of formula (I) formed from non-toxic mineral or organic acids such as, for example, hydrobromic acid, hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, acetic acid, succinic acid, tartaric acid, citric acid, maleic acid, hydroxymaleic acid, benzoic acid, fumaric acid, toluenesulphonic acid, isethionic acid and the like. The various quaternary ammonium salts of the compounds of formula (I) are also included in this category of

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compounds of the invention. In addition, the expression "pharmacologically acceptable salts of a compound of formula (I) with an acid function" means the usual salts of the compounds of formula (I) formed from non-toxic mineral or organic bases such as, for example, the hydroxides of alkali metals and of alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

As mentioned above, the compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13

In this respect, their use is recommended in the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended during the treatment of any pathology in which a destruction of extracellular matrix tissue is involved, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and certain cancers

Selectivity of the compounds of formula (I) for the enzyme MMP-13

Most of the matrix metalloprotease inhibitors described in the prior art are non-selective inhibitors, capable of simultaneously inhibiting several matrix metalloproteases. For example, compounds such as CGS-27 023A and AG-3340 (Montana and Baxter (2000)) inhibit both MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13, i.e. these compounds of the prior art inhibit MMPs of both collagenase, gelatinase and stromelysin type.

It has been shown according to the invention that compounds of general formula (I) are selective inhibitors of MMP-13. "Selective inhibitors of MMP-13" refers to a compound of formula (I) which have an IC_{50} for MMP-13 at least 5 times lower than the IC_{50} for a MMP distinct from MMP-13, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times, 100 times or 1000 times lower than the IC_{50} value for a MMP distinct from MMP-13.

A MMP distinct from MMP-13 refers preferably to a matrix metalloprotease selected from MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14

In particular, it has been shown according to the invention that the compounds of general formula (I), and more particularly the family of compounds given as examples in the present description, have an IC_{50} value for the enzyme MMP-13 which is often 1 000 times lower than the value of their IC_{50} for other matrix metalloproteases, in particular MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14

The result of this is that the compounds of general formula (I) according to the invention are particularly useful in the treatment of complaints mainly associated with a physiological imbalance between the MMP-13 enzymes and their natural tissue inhibitors

PHARMACEUTICAL FORMULATION OF THE COMPOUNDS OF THE INVENTION

A subject of the present invention is also a pharmaceutical composition comprising a compound of general formula (I) as defined above and a pharmaceutically acceptable excipient.

The invention also relates to the use of a compound of general formula (I) as defined above for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of matrix metalloprotease, and more particularly a disease or complaint involving therapy by inhibition of type-13 matrix metalloprotease (MMP-13) such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers

The invention also relates to a method for treating a pathology associated with an imbalance in the activity of MMPs, and more specifically of MMP-13, the said method comprising a step during which a pharmaceutically effective amount of an MMP-inhibitor compound according to the invention, or a pharmaceutical composition containing this compound, is administered to a patient requiring such a treatment.

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Among the various pathologies associated with an imbalance in MMP activity, an MMP-13-inhibitor compound of general formula (I) according to the invention is particularly useful for treating all pathologies brought about by a degradation of extracellular matrix tissue, and more particularly for treating rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancer

In an entirely preferred manner, a compound of general formula (I) as defined according to the invention will be used, preferably to treat arthritis, osteoarthritis and rheumatoid arthritis

The compounds of the invention are administered in the form of compositions that are suitable for the nature and gravity of the complaint to be treated. The daily dosage in man is usually between 2 mg and 1 g of product which may be absorbed in one or more dosage intakes. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula I) and 40% to 99.5% by weight of pharmaceutically acceptable vehicle

The compositions of the present invention are thus prepared in forms that are compatible with the desired route of administration. By way of example, the following pharmaceutical forms may be envisaged, although the list given below is not limiting:

1) Forms for oral administration

Drinkable solutions, suspensions, sachets of powder for drinkable solution, sachets of powder for drinkable suspension, gastro-resistant gel capsules, sustained-release forms, emulsions, HPMR capsules or gel capsules, lyophilizates to be melted under the tongue

2) Forms for parenteral administration

Intravenous route

Aqueous solutions, water/cosolvent solutions, solutions using one or more solubilizing agents, colloidal suspensions, emulsions, nanoparticulate suspensions which can be used for the injection of sustained-release forms, dispersed forms and liposomes.

Subcutaneous/intramuscular route

- 5 In addition to the forms which can be used intravenously and which can also be used for the subcutaneous and intramuscular routes, other types of forms such as suspensions, dispersed forms, sustained-release gels and sustained-release implants may also be used.

3) Forms for topical administration

- 10 Among the most common topical forms that are distinguished are creams, gels (aqueous phases gelled with polymers), patches, which are dressings to be stuck directly onto the skin and which can be used to treat dermatosis without percutaneous penetration of the active substance, sprays, emulsions and solutions

4) Forms for pulmonary administration

- 15 Forms such as solutions for aerosols, powders for inhalers and other suitable forms are distinguished in this category

5) Forms for nasal administration

This especially relates herein to solutions for drops

6) Forms for rectal administration

Suppositories and gels will be selected, inter alia.

- 20 It is also possible to envisage using forms allowing the administration of ophthalmic solutions or allowing the vaginal administration of the active principle.
- Another important category of pharmaceutical form which may be used in the context of the present invention relates to forms for improving the solubility of the active principle. By way of example, it may be envisaged to use aqueous solutions of cyclodextrin, and
- 25 more particularly forms comprising hydroxypropyl- β -cyclodextrin. A detailed review of this type of pharmaceutical form is presented in the article published under the reference

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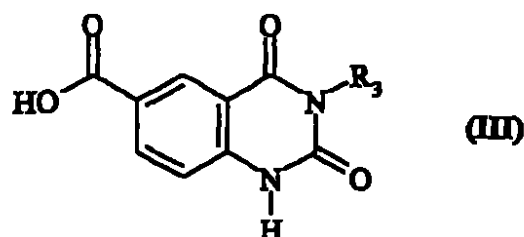
Journal of Pharmaceutical Sciences, 85 (11), 1142-1169 (1996), and incorporated into the present patent application by reference

The various pharmaceutical forms recommended above are described in detail in the book "Pharmacie galénique" by A. Lehur (published by Masson, 1992 (6th edition)), which is

5 incorporated into the present patent application by reference.

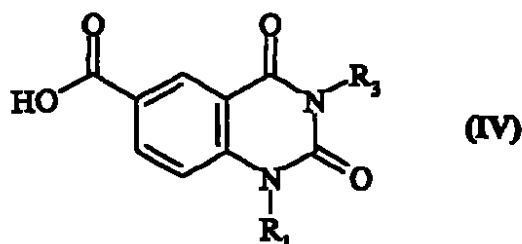
INTERMEDIATE COMPOUNDS

The present invention also relates to an intermediate compound of general formula (III)



in which R³ has the same meaning as for the compound of general formula (I)

10 According to another aspect, the present invention also relates to an intermediate compound of general formula (IV)



in which R₁ and R₃ have the same meaning as that defined above for the compound of general formula (I).

15 PROCESSES FOR SYNTHESIZING THE COMPOUNDS OF GENERAL FORMULA (I)

Throughout this application the following abbreviations have the meanings listed below

DEAD Diethyl azodicarboxylate

DIPEA *N,N*-diisopropylethylamine

DMF *N,N*-dimethylformamide

NMP 1-methyl-2-pyrrolidinone

THF tetrahydrofuran

TOTU O-[(ethoxycarbonyl)cyanomethylensamino]-*N,N,N',N'*-tetramethyluonium
5 tetrafluoroborate

EDCL 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

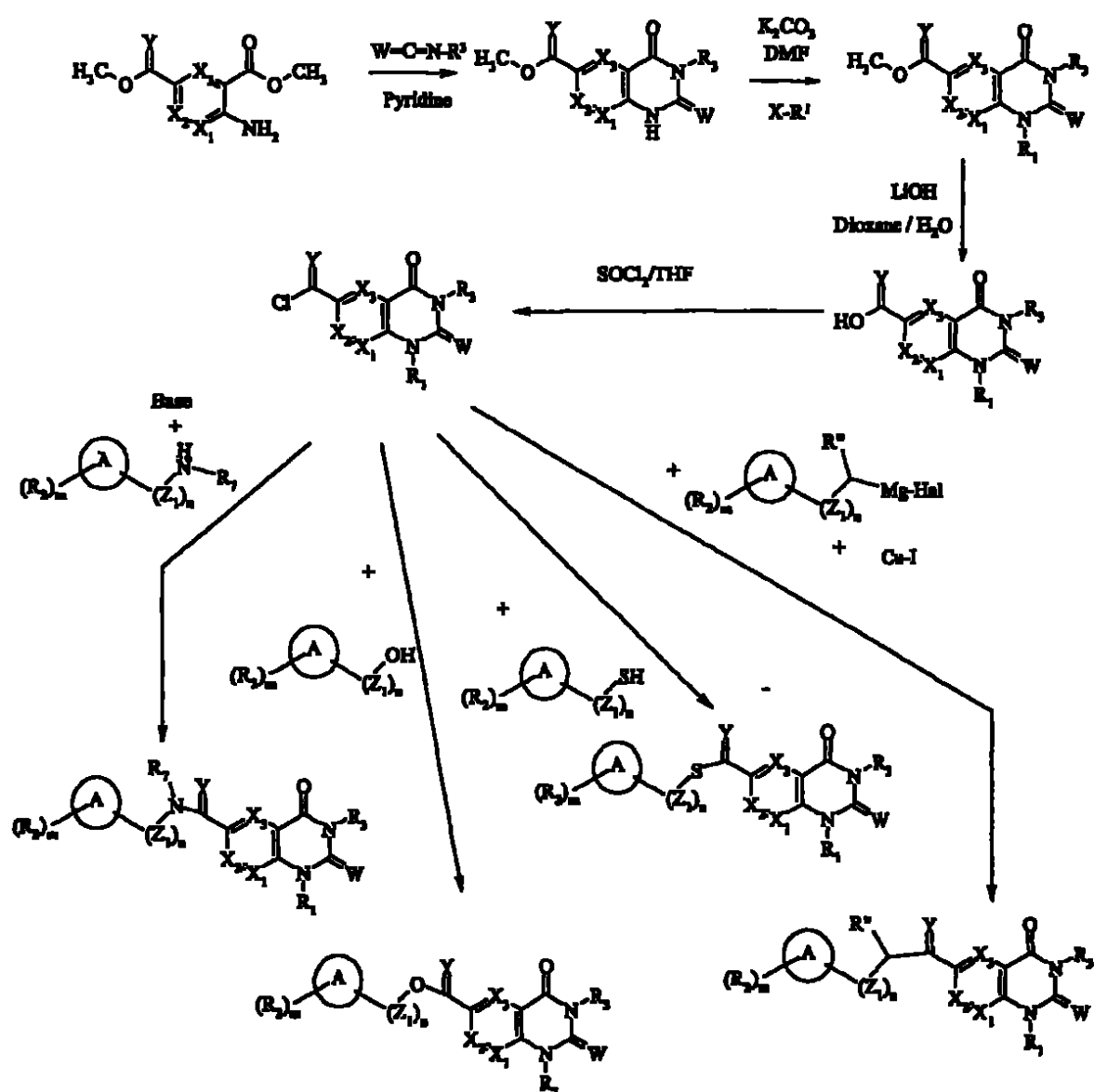
HOBt 1-hydroxybenzotriazole hydrate

The compounds according to the present invention can be obtained by carrying out several
synthetic processes. Some of these synthetic processes are described below

10 **A) General process**

A general process for the synthesis of the compounds of general formula (I) is described in
the following scheme

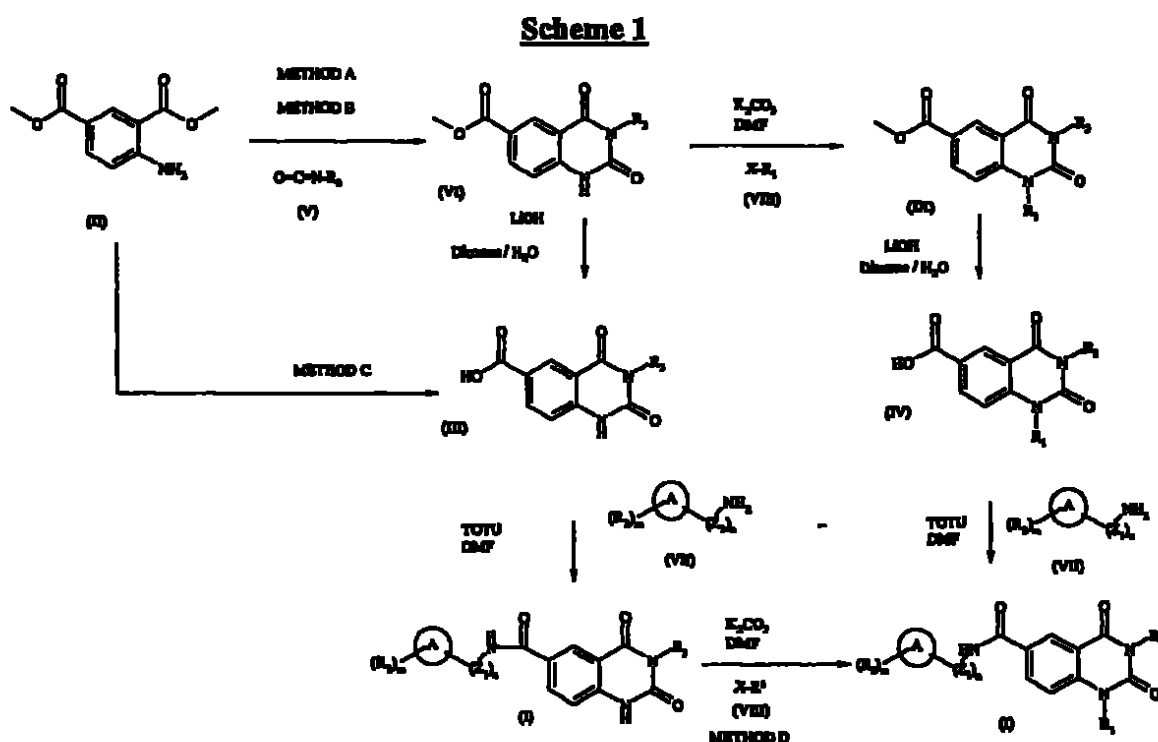
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in which R_1 is hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl or heteroaryl, R_2 is (C_1-C_6) alkyl, aryl, aryl (C_1-C_6) alkyl, aromatic or non-aromatic heterocycle or cycloalkyl, and R_3 , X_1 , X_2 , X_3 , A , W , Y , Z_1 , n and m have the same meaning as that defined above for the compound of formula (I)

B) Synthetic process No. 1

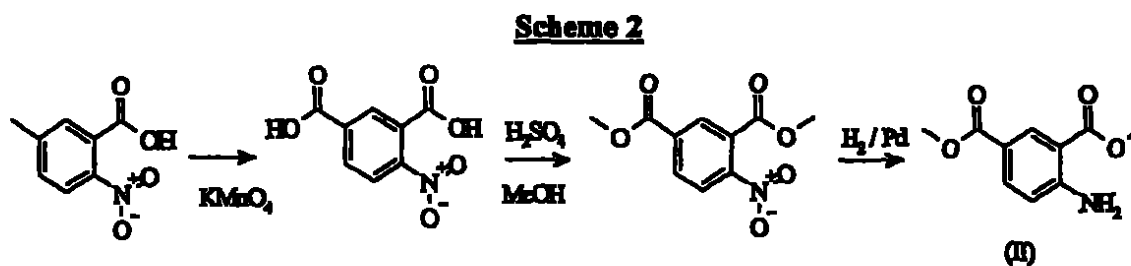
The compounds of the present invention may be obtained firstly by the method represented in Scheme 1 below



- 5 in which each of the generic substituents is as defined for the compound of general formula (I)

The intermediate compound of formula (II) which constitutes the starting material for the synthetic process illustrated by Scheme 1 above may be prepared in accordance with Scheme 2 below

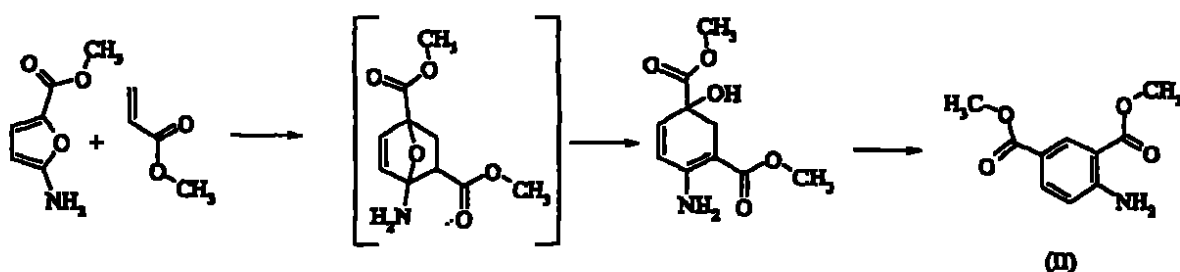
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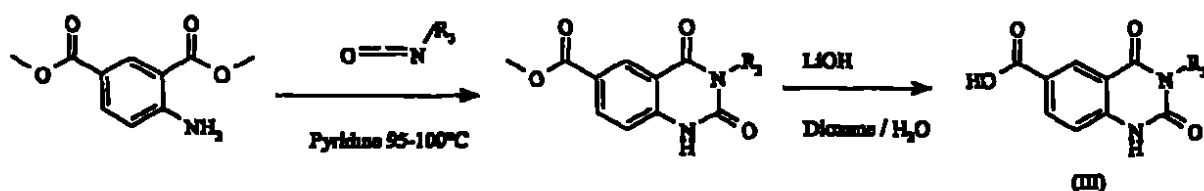
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The intermediate compound of formula (II) which constitutes the starting material in the process to synthesize the compounds of general formula (I) according to the invention as illustrated in Scheme 1 above may also be prepared according to the process illustrated in Scheme 3 below

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Scheme 3

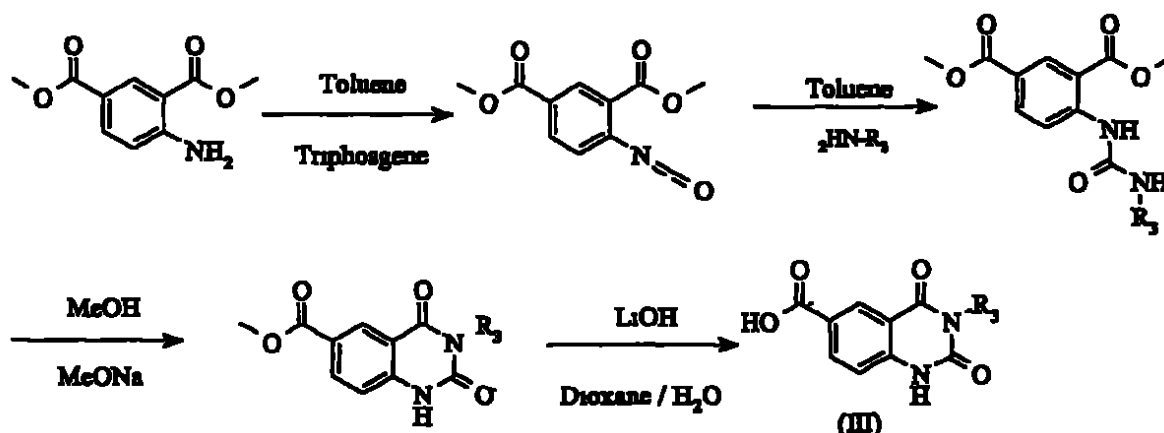
The compound of general formula (III) may be prepared, in accordance with the process described in Scheme 1 above, from the compound of formula (II), according to the synthetic Scheme 4 (Method A) below

Scheme 4 / Method A

10

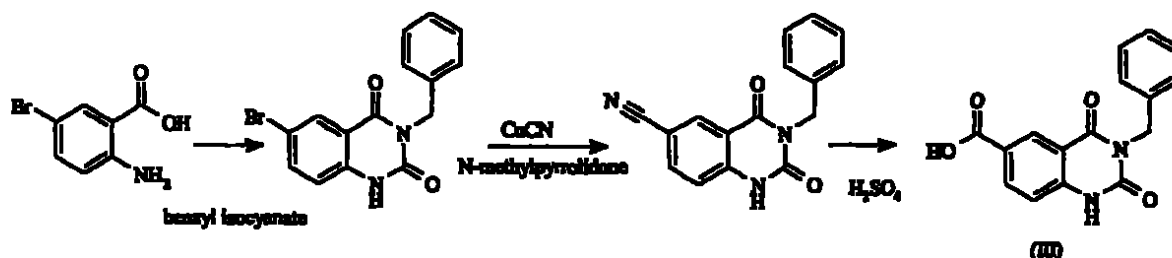
in which R_3 is as defined above for the compound of general formula (I)

According to another aspect, the intermediate compound of formula (III) may be prepared, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method B, as illustrated in Synthetic Scheme 5 below

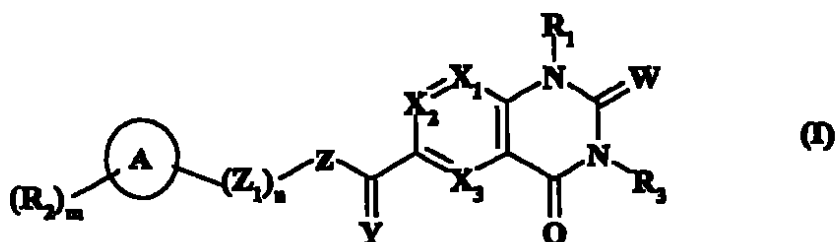
Scheme 5 / Method B

in which R_3 is as defined for the compound of general formula (I)

According to yet another aspect, an intermediate compound of general formula (III), in which R_3 is a benzyl radical, may be obtained, in accordance with the synthetic process illustrated in Scheme 1 above, according to Method C illustrated in Synthetic Scheme 6 below

Scheme 6 / Method C

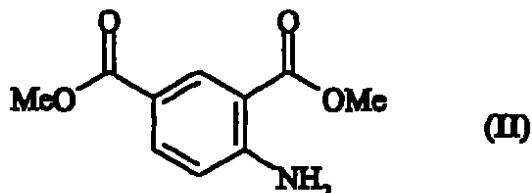
Consequently, a subject of the invention is also a process for manufacturing a compound of general formula (I)



in which R_1 , R_2 , R_3 , Z_1 , A , n and m are as defined in the summary of the invention, X_1 , X_2 and X_3 are CH , Y is O , Z is N-R_7 and W is O ,

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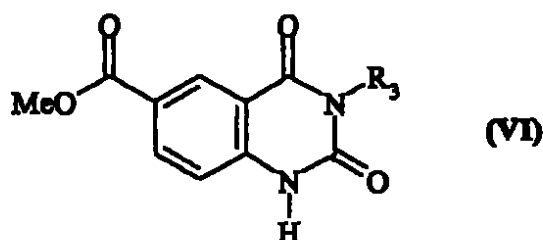
the said process being characterized in that it comprises the reaction of a compound of formula (II)



with pyridine and the compound of general formula (V)

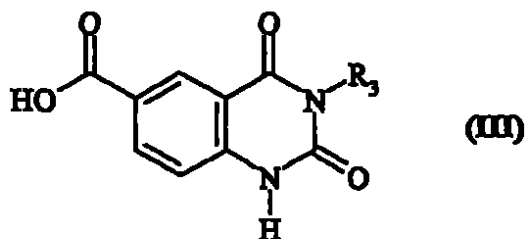


in which R_3 is as defined in the summary of the invention, to give the compound of general formula (VI)

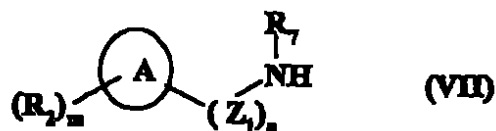


in which R_3 is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which R_3 is as defined in the summary of the invention.



The above process is also characterized in that the compound of general formula (III) in which R_3 is as defined for the compound of general formula (I), is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII)

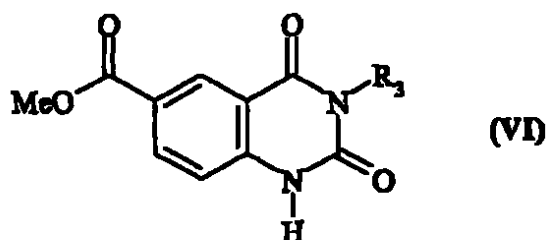


in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A , R_2 , Z_1 , m and n are as defined for the compound of general formula (I),

to give the compound of general formula (I) in which R_1 represents H, X_1 , X_2 and X_3 are CH, Y is O, Z is N- R_7 , W is O, and A, R_2 , R_3 , Z_1 , m and n are as defined hereinbefore

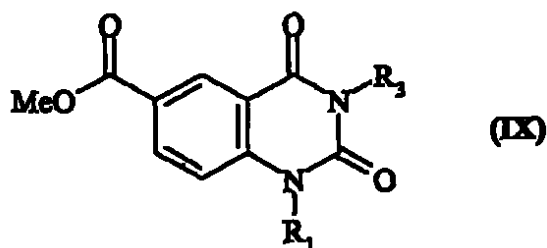
The present invention also relates to a process for manufacturing a compound of general formula (I) in which R_1 , R_2 , R_3 , A, Z_1 , m and n are as defined for the compound of general formula (I), X_1 , X_2 and X_3 are CH, W is O, Y is O and Z is N- R_7 ,

the said process being characterized in that a compound of general formula (VI)



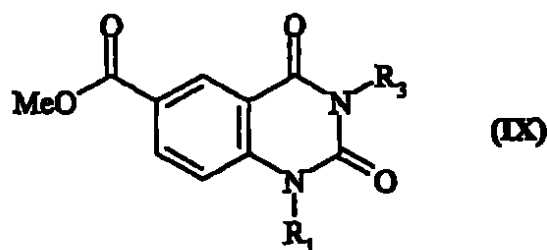
in which R_3 is as defined in the summary of the invention,

is reacted, in the presence of a base, with compound (VIII) of general formula X- R_1 , in which R_1 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (IX)



in which R_1 and R_3 are as defined hereinbefore.

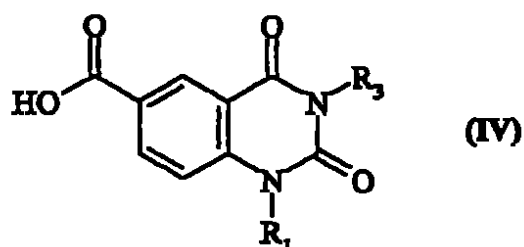
The above process is also characterized in that the compound of general formula (IX)



is reacted in the presence of LiOH to give the compound of general formula (IV)

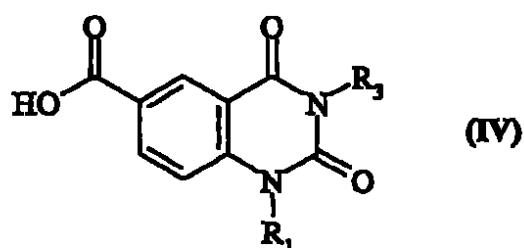
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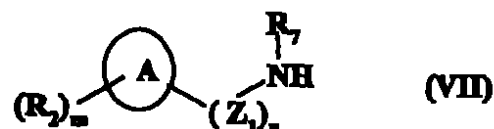


in which R_1 and R_3 are as defined hereinbefore

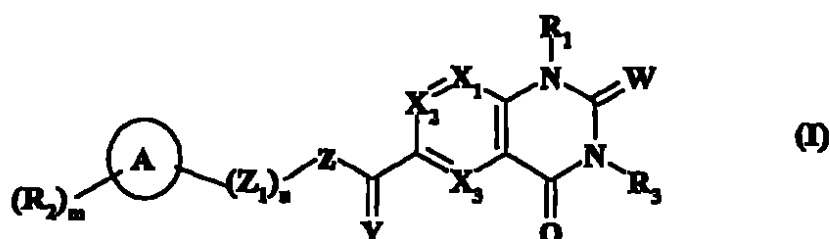
The above process is also characterized in that the compound of general formula (IV)



- 5 in which R_3 is as defined in the compound of general formula (I),
is reacted, in the presence of an acid activator such as TOFU, with the compound of
general formula (VII)



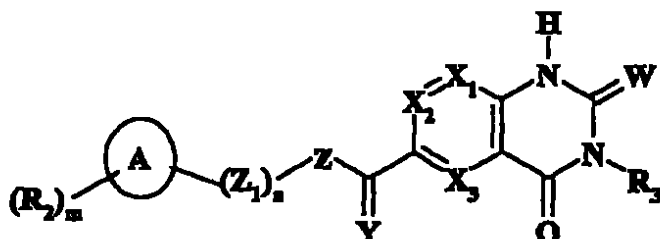
- 10 in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and
heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention, to give
the compound of general formula (I)



in which R_1 , R_2 , R_3 , A, Z_1 , m and n are as defined in the summary of the invention, X_1 , X_2
and X_3 are CH, W is O, Y is O and Z is N- R_7

- 15 Another subject of the present invention is a process for manufacturing the compound of
general formula (I) in which R_1 , R_2 , R_3 , W, X_1 , X_2 , X_3 , A, Z_1 , m and n are as defined for

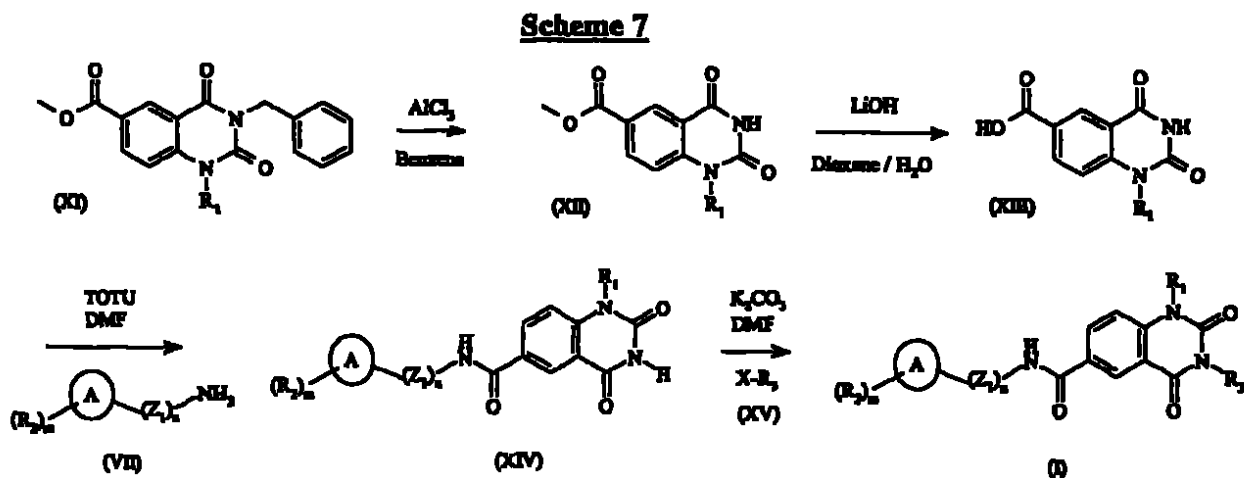
the compound of general formula (I), Y is O and Z is N-R₇, characterized in that a compound of general formula (I) in which R₁ is H,



is reacted, in the presence of a base, with a compound (VIII) of general formula X-R₁, in which R₁ is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which R₁ is as defined in the summary of the invention.

C Synthetic process No. 2

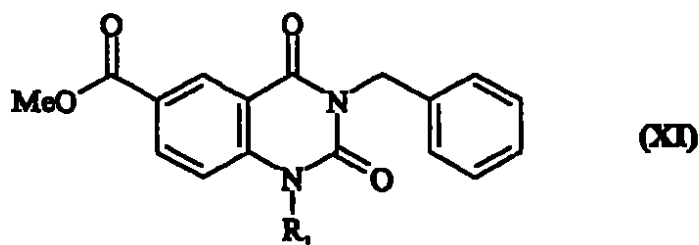
The compounds of the present invention can also be obtained by the method represented in Scheme 7 below



in which each of the generic substituents is as defined for the compound of general formula (I)

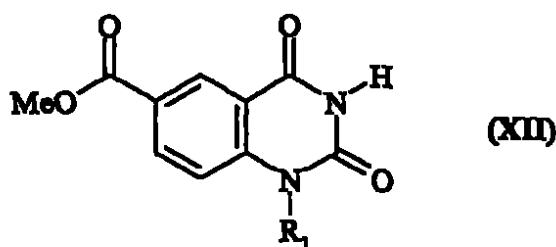
The present invention also relates to a process for manufacturing a compound of general formula (I) in which X₁, X₂ and X₃ are CH, W is O, Y is O, Z is N-R₇, R₁, R₃, A, R₂, Z₁, m

and n are as defined for the compound of general formula (I) characterized in that a compound of general formula (XI)



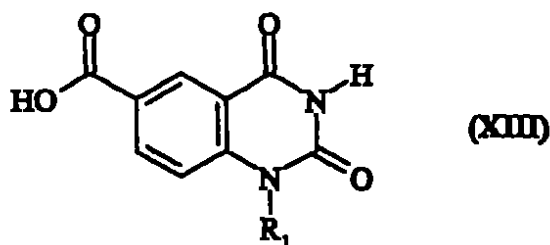
in which R_1 is as defined hereinbefore,

5 is reacted with $AlCl_3$ in a solvent such as benzene, to give the compound of general formula (XII)



in which R_1 is as defined hereinbefore.

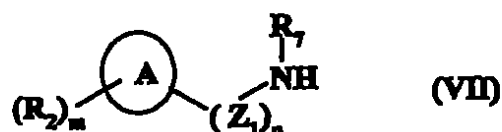
10 The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XII) is reacted in the presence of $LiOH$ and a mixture of dioxane/ H_2O to give the compound of general formula (XIII)



in which R_1 is as defined hereinbefore.

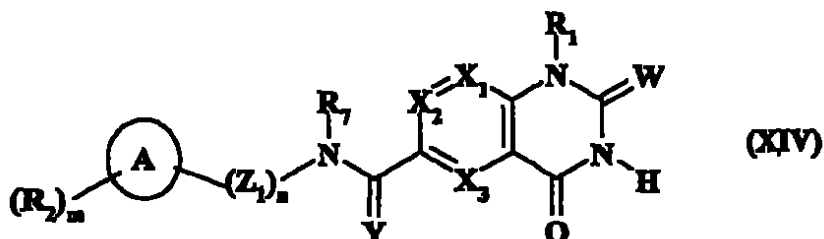
15 The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIII) is reacted, in the presence of an acid activator such as TOTU with the compound of general formula (VII)

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in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention,

to give the compound of general formula (XIV) in which X_1 , X_2 and X_3 are CH, W is O, Y is O, and R_7 , R_1 , A, R_2 , Z_1 , m and n are as defined hereinbefore



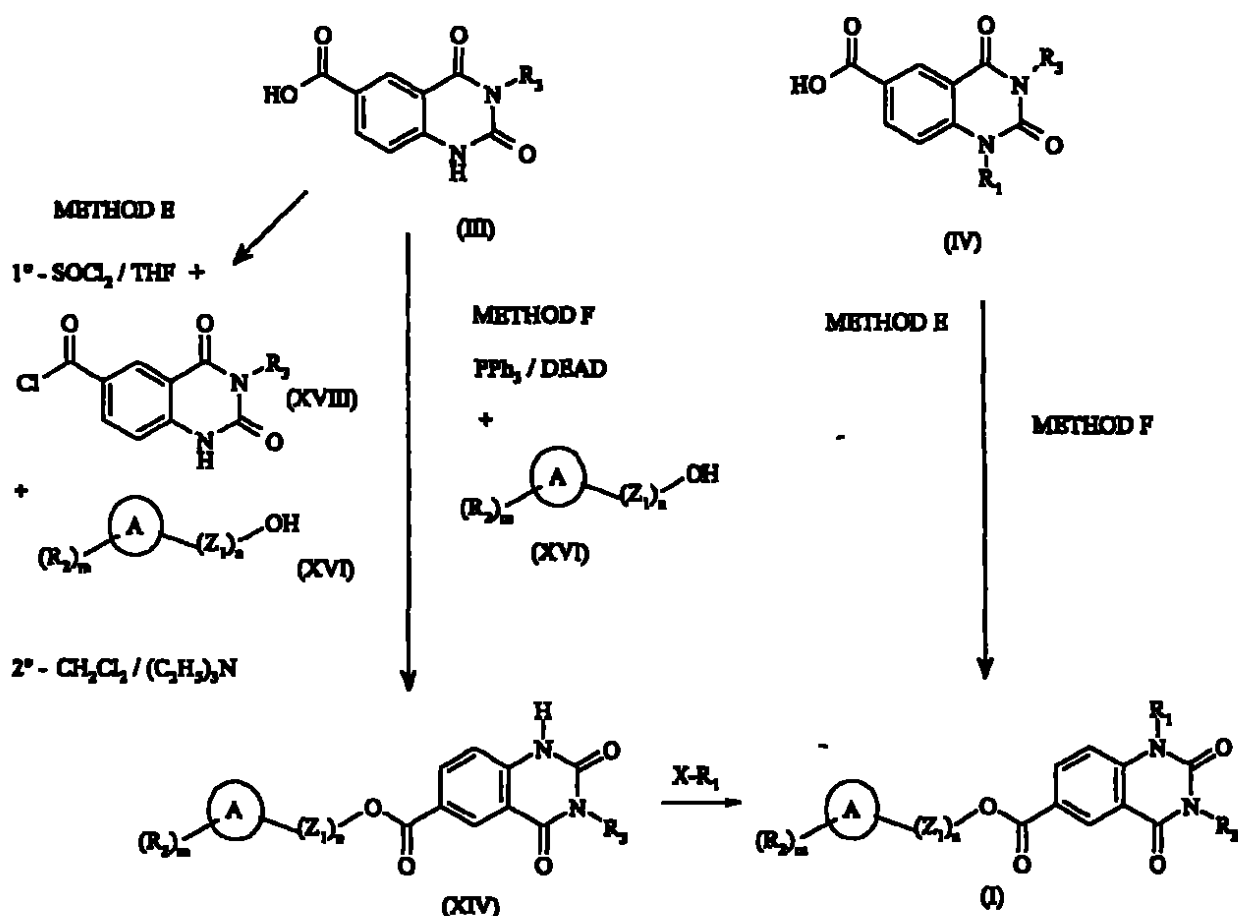
The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XIV) is reacted with compound (XV) of general formula $X-R_3$, in which R_3 is as defined in the summary of the invention and X is a leaving group such as halogen, to give the compound of general formula (I) in which X_1 , X_2 and X_3 are CH, W is O, Y is O, Z is N- R_7 , and R_7 , R_1 , A, R_2 , Z_1 , m and n are as in the compound of general formula (I)

D Preparation process No. 3

The compounds of general formula (I) of the present invention may also be obtained by the method represented in Scheme 8 below

20

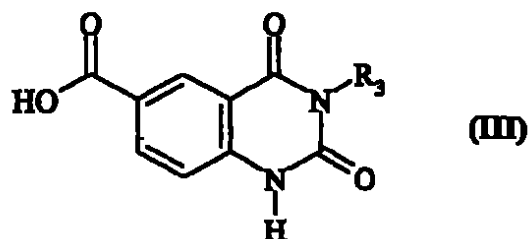
Scheme 8



In this scheme, each generic substituent is as defined for the compound of general formula (I) above.

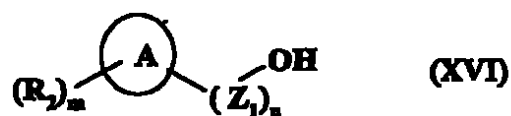
5

Thus, the present invention also relates to a process for manufacturing a compound of general formula (I) as defined above in which X_1 , X_2 and X_3 are CH, W is O, Y is O and Z is O, characterized in that a compound of general formula (III)

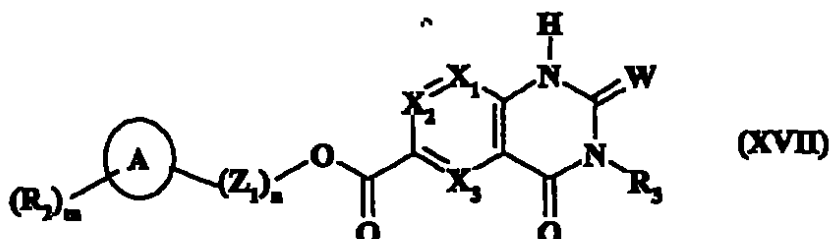


in which R_3 is as defined in the compound of general formula (I), is reacted with a compound of general formula (XVI)

10



in which A, R₂, Z₁, m and n are as defined in the compound of general formula (I),
to give a compound of general formula (XVII)



5 in which A, R₂, R₃, Z₁, m and n are as defined in the summary of the invention, X₁, X₂ and X₃ are CH, and W is O

According to the process for manufacturing a compound of general formula (I) above, the
said process also comprises a step in which the compound of formula (XVII) is reacted, in
the presence of a base, with compound (VIII) of general formula X-R₁, in which R₁ is as
10 defined in the summary of the invention and X is a leaving group such as halogen, to give
the compound of general formula (I) in which X₁, X₂ and X₃ are CH, W is O, Y is O, Z is
O, and A, R₂, R₃, R₁, Z₁, m and n are as defined in the summary of the invention

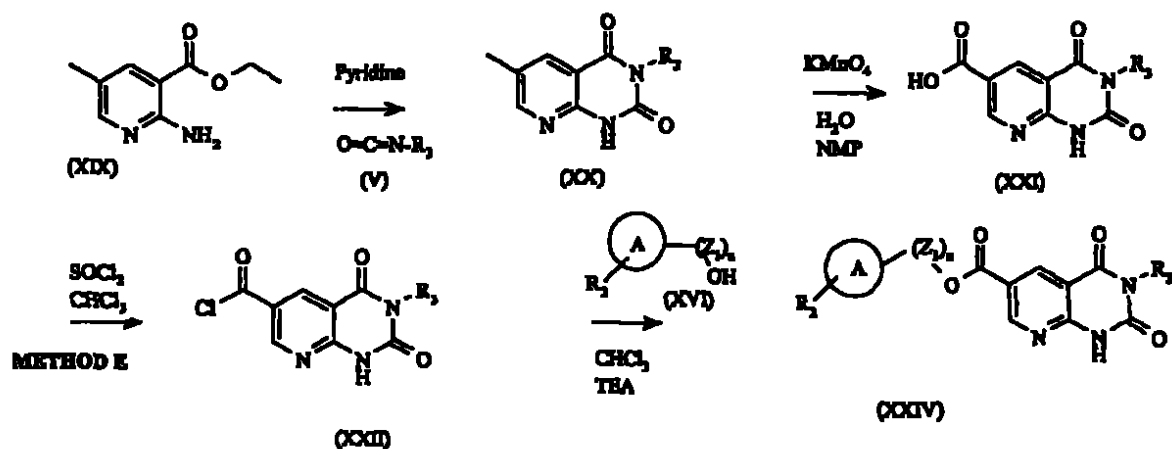
The present invention also relates to a process for manufacturing a compound of general
formula (I) as defined above, characterized in that it comprises a step in which a compound
15 of general formula (IV) is reacted with a compound of general formula (XVI) to give a
compound of general formula (I) in which X₁, X₂ and X₃ are CH, W is O, Y is O and Z is
O

E. Preparation process No 4

20 The compounds of the present invention, and most particularly the compounds of the
invention which constitute pyrimidine esters, may be obtained by the method represented in
Scheme 9 below

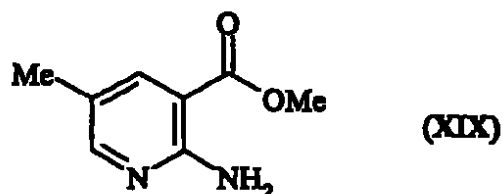
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Scheme 9

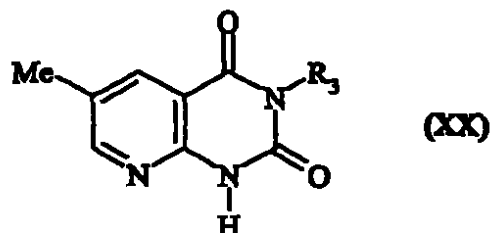


in which each of the generic substituents on the intermediate compounds has the same meaning as for the compound of general formula (I) as defined in the summary of the invention.

Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which X_2 and X_3 are CH , X_1 is N , Z is O and Y is O , characterized in that the said process comprises a step in which a compound of general formula (XIX)

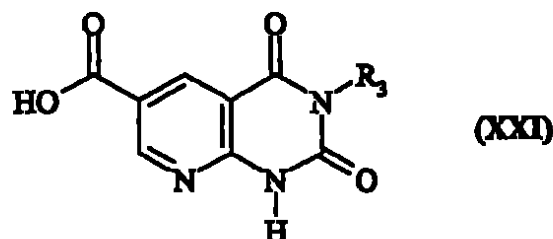


is reacted with pyridine and a compound (V) of general formula $O=C-N-R_3$ in which R_3 is as defined in the compound of general formula (I), to give a compound of general formula (XX)



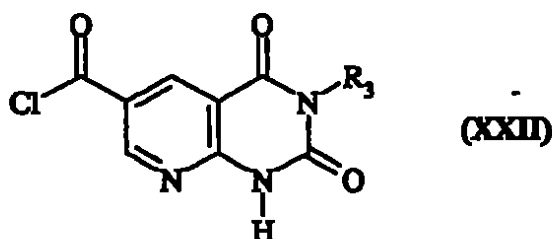
in which R_3 is as defined hereinbefore.

The process for manufacturing a compound of general formula (I) above is also characterized in that it comprises a step in which the compound of general formula (XX) is reacted in the presence of KMnO_4 to give the compound of general formula (XXI)



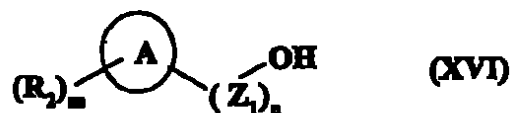
5 in which R_3 is as defined hereinbefore.

The above process is also characterized in that it comprises a step in which a compound of general formula (XXI) is reacted in the presence of SOCl_2 and CHCl_3 to give the compound of general formula (XXII)



10 in which R_3 is as defined hereinbefore.

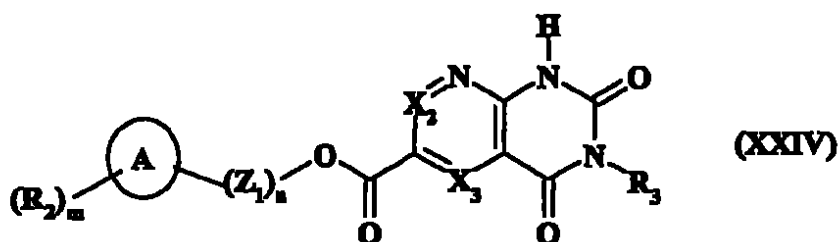
The process for manufacturing a compound of general formula (I) according to the invention is also characterized in that it comprises a step in which the compound of formula (XXII) is reacted with the compound of general formula (XVI)



15 in which A , R_2 , Z_1 , m and n are as defined in the compound of general formula (I), to give the compound of general formula (XXIV) in which X_2 and X_3 are CH and A , n , m , Z_1 , R_2 and R_3 are as defined in the summary of the invention/

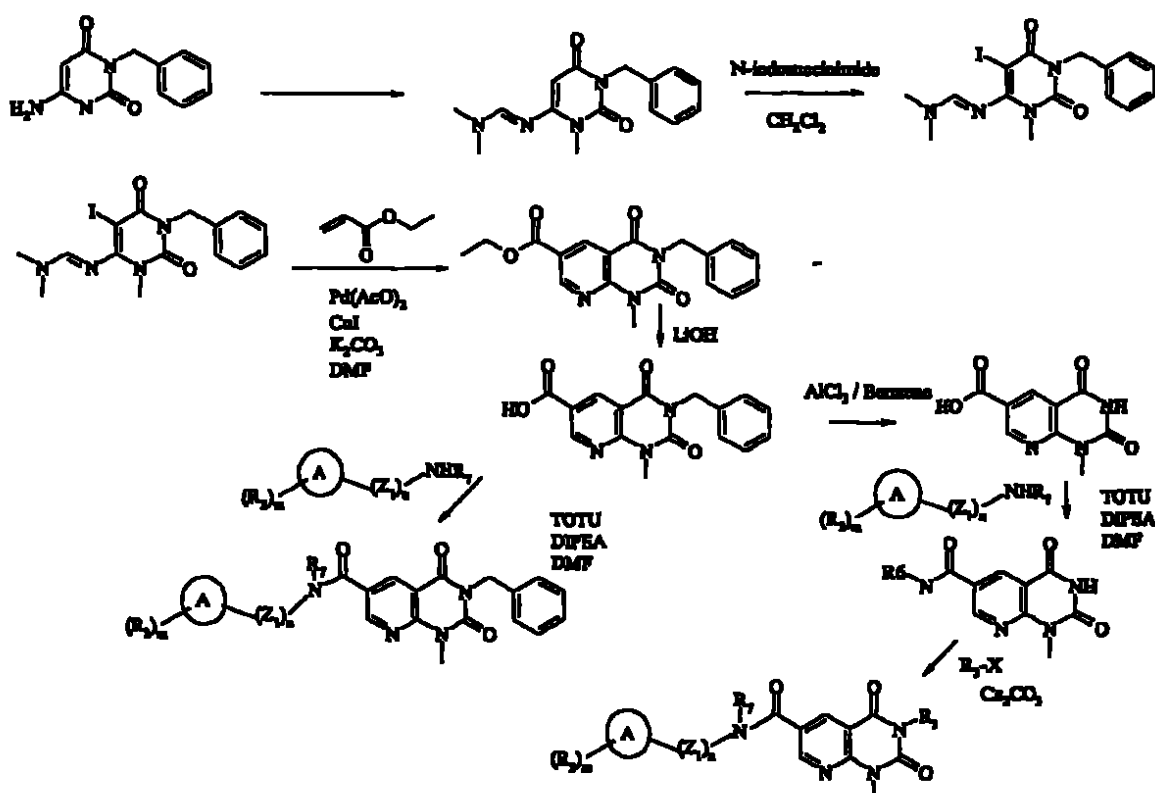
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The compounds of the present invention which constitute pyridine amide can also be obtained by the method represented in scheme 10 below

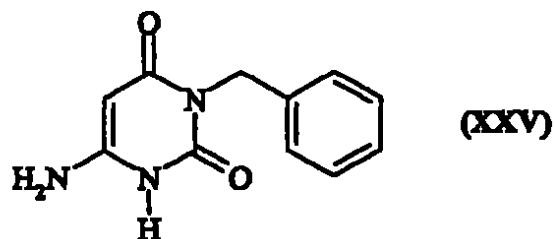
Scheme 10



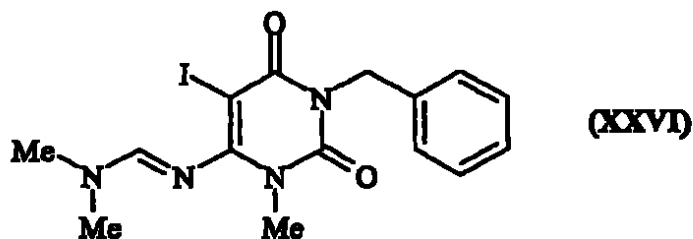
5

Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which X_2 and X_3 are CH, X_1 is N, Z is $-NR_7$ in which R_7 is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXV)

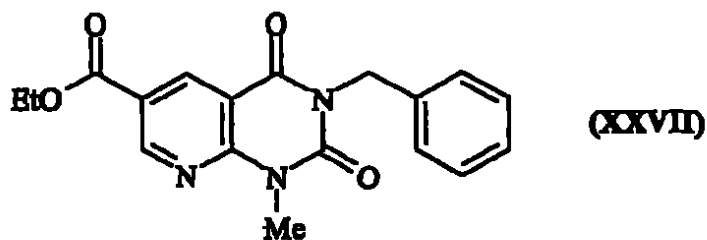
52



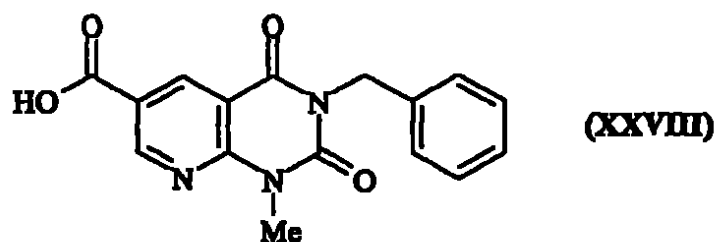
is reacted in a first step with N,N'-dimethylformamide dimethyl acetal under reflux of DMF, and in a second step with N-iodosuccinimide, to give a compound of formula (XXVI)



followed by reacting the compound of formula (XXVI) with ethyl acrylate in the presence of palladium diacetate, CuI and a base, to give the compound of general formula (XXVII)



followed by reacting the compound of formula (XXVII) in the presence of LiOH to give the compound of general formula (XXVIII)

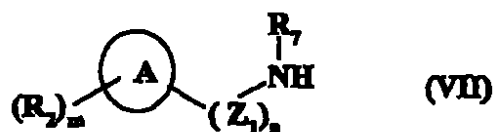


the said compound of formula (XXVIII)

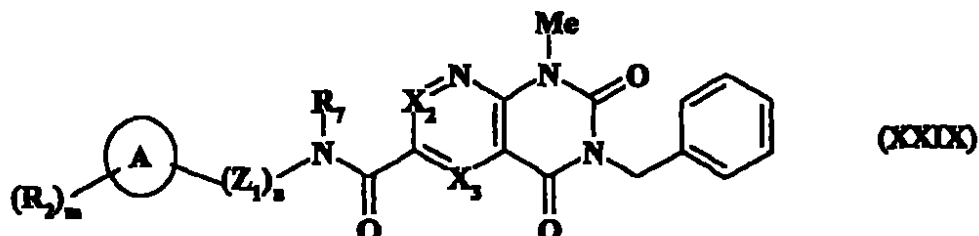
- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII)

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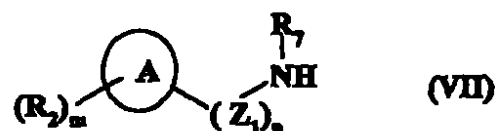
in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXIX)



5

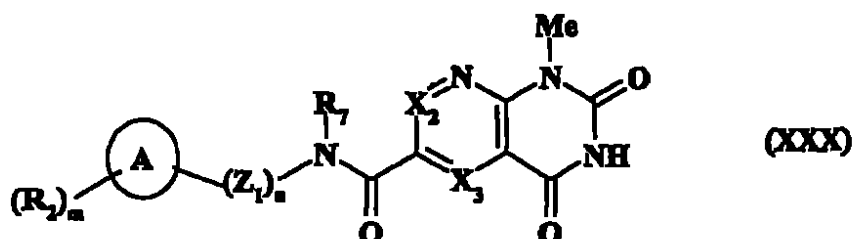
in which A, R_2 , R_7 , Z_1 , m and n are as defined hereinbefore, and X_2 and X_3 represents each -CH group,

- or is reacted in a first step with AlCl_3 in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII)



10

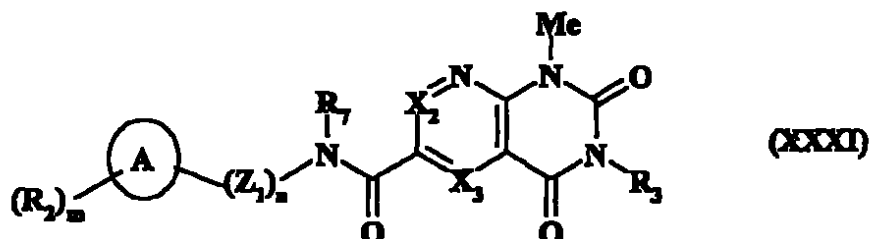
in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXX)



15

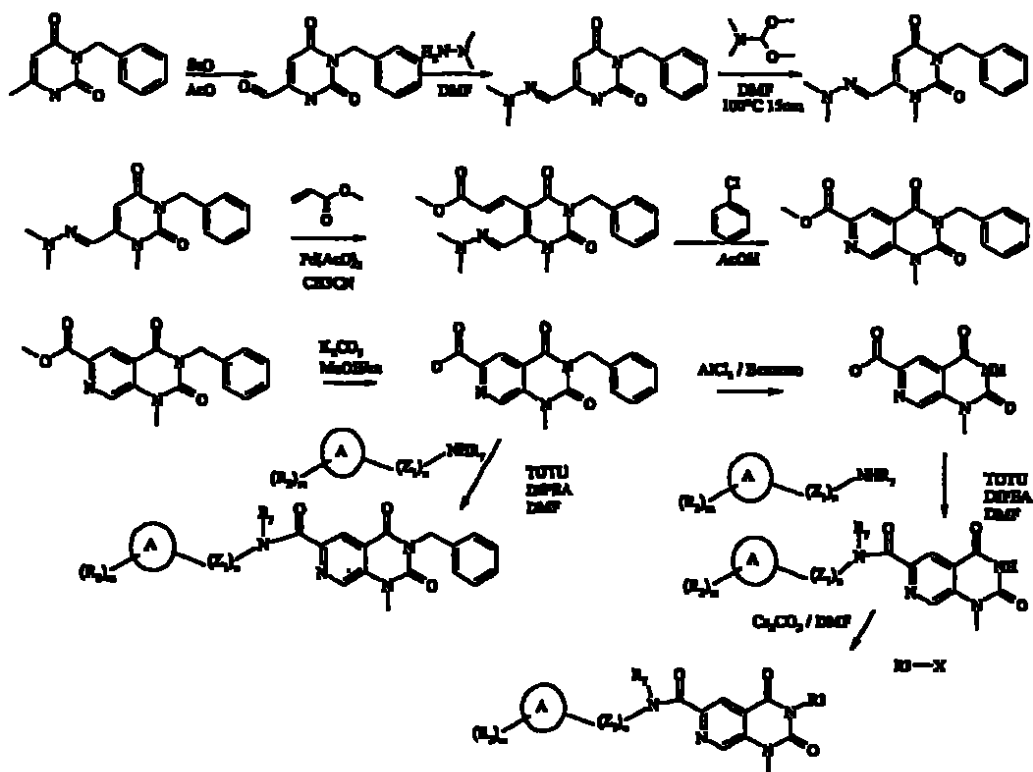
in which A, R_2 , R_7 , Z_1 , m and n are as defined hereinbefore, and X_2 and X_3 represents each -CH group,

followed by reacting the compound of formula (XXX) with a compound of formula R_3-X in which R_3 is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXI)



- 5 The compounds of the present invention which constitute pyridine amide, and particularly pyrido[3,4-d]pyrimidine derivatives, can also be obtained by the method represented in scheme 11 below

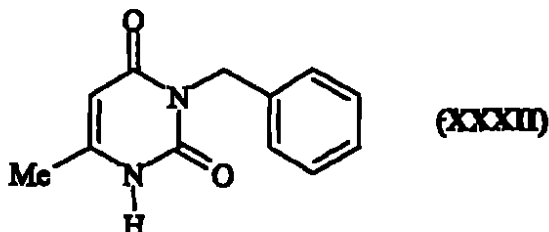
Scheme 11



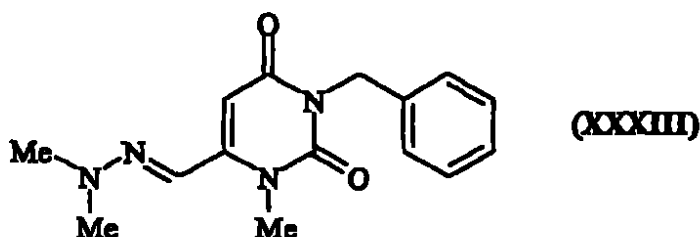
- 10 Consequently, a subject of the present invention is also a process for manufacturing a compound of general formula (I) in which X_1 and X_3 are CH, X_2 is N, Z is $-NR_7$ in which

55

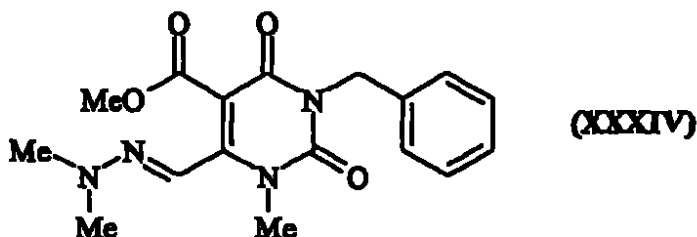
R₇ is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXXII)



5 is reacted in a first step with selenium dioxide in the presence of acetic acid, in a second step with dimethylhydrazine, and in a third step with N,N'-dimethylformamide dimethylacetal under reflux of DMF, to give a compound of formula (XXXIII)

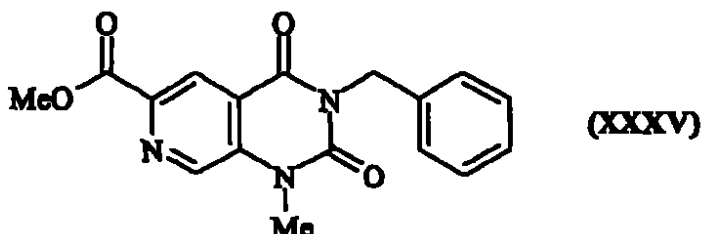


followed by reacting the compound of formula (XXXIII) with methyl acrylate in the presence of palladium diacetate, to give the compound of general formula (XXXIV)



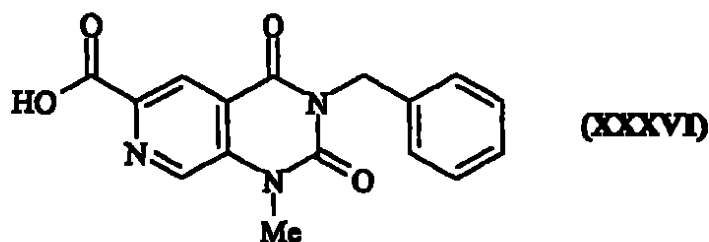
10

followed by reacting the compound of formula (XXXIV) with chlorobenzene and acetic acid to give the compound of formula (XXXV)



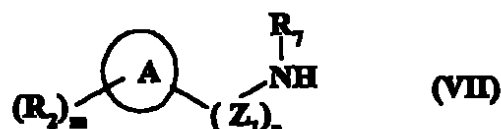
15

followed by reacting the compound of formula (XXXV) in the presence of a base to give the compound of general formula (XXXVI)

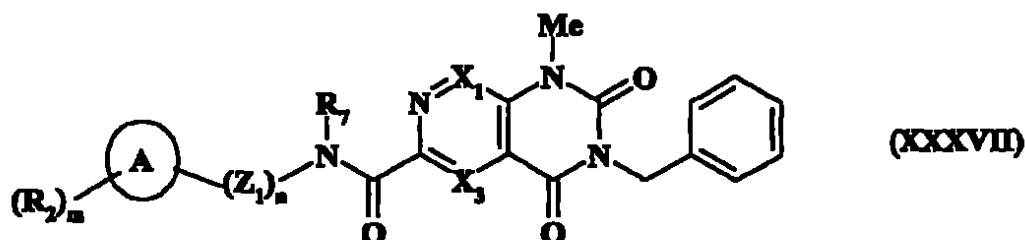


the said compound of formula (XXXVI)

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII)

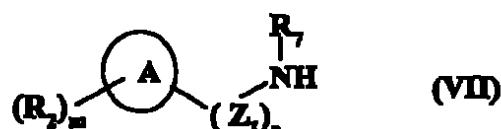


in which R₇ is selected from hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, cycloalkyl, aryl and heteroaryl, and A, R₂, Z₁, m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVII)

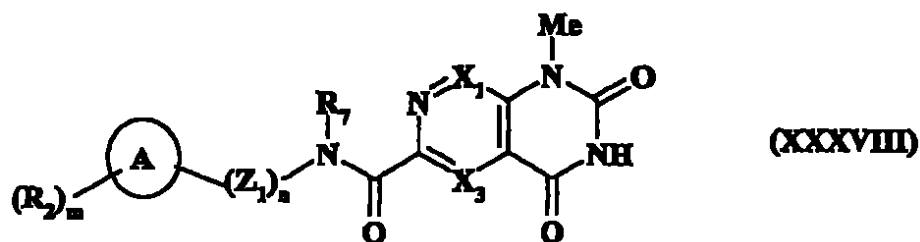


in which A, R₂, R₇, Z₁, m and n are as defined herembefore, and X₁ and X₃ represents each -CH group,

- or is reacted in a first step with AlCl₃ in the presence of benzene, and in a second step in the presence of an acid activator such as TGTU, with the compound of formula (VII)

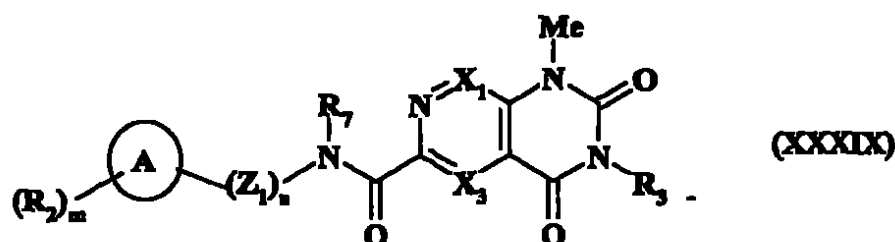


in which R₇ is selected from hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, cycloalkyl, aryl and heteroaryl, and A, R₂, Z₁, m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVIII)



in which A, R₂, R₇, Z₁, m and n are as defined hereinbefore, and X₁ and X₃ represents each -CH group,

5 followed by reacting the compound of formula (XXXVIII) with a compound of formula R₃-X in which R₃ is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXIX)



The present invention is also illustrated, without being limited thereby, in the examples which follow

10 EXAMPLES

Preparation A. Dimethyl 4-aminophthalate

Preparation according to Scheme 2

Step 1-2 4-Nitroisophthalic acid

15 25 g (138 mmol) of 5-methyl-2-nitrobenzoic acid are suspended in 300 ml of water 5 g (89.1 mmol) of KOH are added for dissolution. The medium is heated to 90°C and 158 g of KMnO₄ (414 mmol) are added portionwise, mixing with H₂O. After 3 hours, the reaction medium is filtered through Celite and the filtrate is acidified to pH 1 with concentrated HCl. The precipitate obtained is filtered off and dried under vacuum.

Weight = 15.3 g, Yield = 53%

NMR. DMSO ^1H δ (ppm) 5.62-5.70 (d, 1H), 7.88 (d, 1H), 8.16 (s, 1H)

Step 2-2 Dimethyl 4-nitroisophthalate

12.75 g (60.4 mmol) of 4-nitroisophthalic acid from the above stage and 13 ml of H_2SO_4 and 100 ml of methanol are maintained at reflux overnight. After cooling, the methanol is removed under vacuum. The residue is dissolved in 400 ml of EtOAc. The organic phase is washed with 50 ml of H_2O and then with 50 ml of 5% NaHCO_3 solution.

Drying over MgSO_4 and concentration under vacuum gives a crystalline residue.

Weight = 12.17 g Yield = 84%

NMR. DMSO ^1H δ (ppm) 3.86 (s, 3H), 3.91 (s, 3H), 8.16 (d, 1H), 8.29-8.34 (m, 2H)

Step 3-2 Dimethyl 4-aminoisophthalate

The compound from the above stage is reduced with hydrogen in the presence of palladium as catalyst.

Filtration through Celite and concentration gives

Weight = 5.12 g Yield = 70%

m.p. = 127-128°C

NMR. CDCl_3 ^1H δ (ppm) 3.87 (s, 3H), 3.88 (s, 3H), 6.30 (brs, 2H), 6.65 (d, 1H), 7.89 (dd, 1H), 8.57 (d, 1H)

Preparation according to Scheme 3 - J. Org. Chem., 1997, 62 (12), 4088-4096

Step 1-3 Dimethyl 4-amino-1-hydroxycyclohexa-3,5-diene-1,3-dicarboxylate

526 ml of benzene and 250 ml of methyl acrylate are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under inert atmosphere and protected from moisture, followed by 10 g (70.8 mmol) of methyl 5-amino-2-furan carboxylate. The mixture is brought to reflux and maintained for 24 hours. The reaction medium is concentrated to dryness on a rotavapor at 50°C under a vacuum of 20 mm Hg. The residue obtained is purified by flash chromatography using dichloromethane progressively enriched with ethyl acetate as solvent. The product is obtained as follows

Weight = 15 g of a yellow precipitate Yield = 93%

TLC $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 70/30 v/v $R_f = 0.35$

m.p. = 101.3°C

NMR. CDCl_3 ^1H δ (ppm) 2.87 (d,1H), 2.93 (d,1H), 3.20 (s,1H), 3.71 (s,3H), 3.82 (s,3H), 6.02 (d,1H), 5.60-6.40 (brs,2H), 6.17 (d,1H)

5 **Step 2-3 Dimethyl 4-aminoisophthalate**

15 g (66 mmol) of compound obtained in Step 1-3 and 600 ml of benzene are introduced into a 1-litre three-necked flask fitted with a reflux condenser, placed under an inert atmosphere and protected from moisture. 13.8 g (12 ml, 98 mmol) of BF_3 etherate are added with stirring. The mixture is refluxed for 2 minutes and then cooled to room temperature and, after addition of saturated NaHCO_3 solution (pH 9), the phases are separated by settling. The aqueous phase is re-extracted twice with dichloromethane. The organic phases are combined and dried over Na_2SO_4 . After removal of the solvents under vacuum, the 13.8 g of residue are purified by chromatography using dichloromethane as elution solvent. The product is obtained as follows

15 Weight = 8.5 g of a crystalline residue Yield = 62%

TLC CH_2Cl_2 $R_f = 0.30$

m.p. = 130.1°C

NMR. CDCl_3 ^1H δ (ppm) 3.87 (s,3H), 3.88 (s,3H), 6.30 (brs,2H), 6.65 (d,1H); 7.89 (dd,1H), 8.57 (d,1H)

20 **Preparation B. 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

Preparation according to Scheme 4

**Step 1-4 Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline
 -6-carboxylate**

25 4 g (19.1 mmol) of compound of preparation A and 40 ml of pyridine are successively introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture, followed by addition of 3.2 g (24 mmol) of benzyl isocyanate. The colourless solution is stirred and heated at 95-100°C. After 6 hours at this temperature, 1 ml of benzyl isocyanate is added and stirring is then continued at 100°C overnight. The

next day, the reaction medium is cooled and poured into 400 ml of a water + ice mixture, it is left stirring for about 30 minutes and the precipitate obtained is then filtered off. The product is re-stirred at reflux in 150 ml of ethanol. After cooling, the product is filtered off. The product is obtained as follows

5 Weight = 3.7 g Yield = 62%

NMR. DMSO ^1H δ (ppm) 3.75 (s, 3H); 4.95 (s, 2H), 7.1-7.2 (m, 6H), 8.05 (d, 1H), 8.35 (s, 1H), 11.8 (bs, 1H)

Step 2-4 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

10 1.5 g (4.84 mmol) of methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate, 14 ml of dioxane and 48 ml of H_2O are introduced into a 100 ml round-bottomed flask fitted with a reflux condenser. 0.41 g (9.68 mmol) of hydrated lithium hydroxide is added to the suspension with stirring. The mixture is brought to reflux and maintained for about 1 hour (solution). After cooling in an ice bath, the medium is acidified to pH 1 with concentrated hydrochloric acid. The very fine precipitate obtained is
15 filtered off, to give

Weight: 1.3 g Yield = 96%

NMR. DMSO ^1H δ (ppm) 5.1 (s, 2H), 7.2-7.35 (m, 6H), 8.15 (d, 1H), 8.48 (s, 1H), 11.85 (s, 1H), 13.1 (bs, 1H)

Preparation according to Scheme 5

20 **Step 1-5 Dimethyl 4-(3-benzylureido)isophthalate**

10 g (48 mmol) of compound of Preparation A, 200 ml of anhydrous toluene, about 100 mg of animal charcoal and then 12 g (40 mmol) of triphosgene are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The suspension is stirred and maintained at the reflux point of the toluene for 2 hours. The
25 reaction medium is filtered through infusorial earth and then concentrated to dryness at 50°C under a vacuum of about 20 mm Hg. The residue obtained is dissolved in 200 ml of anhydrous toluene and stirred.

4.7 ml (43 mmol) of benzylamine are added to this solution over a few minutes. A precipitate is immediately formed. 200 ml of toluene are added to facilitate stirring, and the
30 mixture is maintained at room temperature overnight. The next day, the precipitate is

filtered off and washed successively with toluene and ether. After drying under vacuum, the product is obtained as follows:

Weight 13.9 g Yield = 84.6%

TLC $\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2 $R_f = 0.35$

5 m.p. = 181.9°C

NMR (DMSO- d_6) ^1H δ (ppm): 3.8 (s, 3H), 3.9 (s, 3H), 4.3 (s, 2H), 7.2-7.4 (m, 5H), 8.0 (d, 1H), 8.3 (s, 1H), 8.5 (s, 1H), 8.55 (d, 1H), 10.2 (s, 1H)

Step 2-5 Methyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

10 13.7 g (40 mmol) of compound obtained in Step 1-5, 300 ml of methanol and then 1.3 g (24 mmol) of sodium methoxide are introduced into a 1-litre one-necked flask fitted with a reflux condenser and protected from moisture. The white suspension is maintained at reflux for 3 hours (the suspension changes form). Half of the methanol is removed on a rotavapor at 50°C under vacuum. The mixture is cooled and acidified to pH 4 with 2 ml of concentrated hydrochloric acid. It is left stirring for 15 minutes while cold and the crystalline residue obtained is then filtered off.

Weight = 12 g Yield = 96.7%

TLC $\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2

$R_f = 0.05-0.2$

20 m.p. = 248.1°C

NMR (DMSO- d_6) ^1H δ (ppm): 3.9 (s, 3H), 5.1 (s, 2H), 7.2-7.4 (m, 6H), 8.15 (d, 1H), 8.45 (s, 1H), 11.9 (bs, 1H)

Step 3-5 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

25 The product is obtained according to the procedure of Step 2-4 of Preparation B using the compound obtained in preceding Step 2-5.

Preparation according to Scheme 6

Step 1-6 3-Benzyl-6-bromo-1H-quinazoline-2,4-dione

10 g (46.3 mmol) of 2-amino-5-bromobenzoic acid, 100 ml of anhydrous pyridine and 6.16 g (46.3 mmol) of benzyl isocyanate are introduced into a 250 ml one-necked flask

fitted with a reflux condenser and protected from moisture. The solution is maintained at reflux with stirring for 36 hours. The reaction mixture is cooled and H₂O is added until the start of precipitation. The mixture is left to crystallize for about 1 hour and the precipitate obtained is then filtered off and washed. The 8 g of crude product are purified by
5 realurrying in refluxing ethanol.

Weight: 3.4 g

NMR = DMSO ¹H δ (ppm) 4.9 (s, 2H), 7.0 (d, 1H), 7.03-7.2 (m, 5H), 7.65 (d, 1H), 7.85 (s, 1H), 11.5 (s, 1H)

Step 2-6 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carbonitrile

10 2.5 g (7.5 mmol) of compound of Step 1-6, 1.215 g (13.6 mmol) of copper cyanide and 22.5 ml of 1-methyl-2-pyrrolidone are introduced into a 50 ml three-necked flask fitted with a reflux condenser and protected from moisture. The beige-coloured solution obtained is refluxed at an internal temperature of 200°C for 1 h 30 min.

The reaction medium is concentrated to dryness at 80°C under a vacuum < 1 mm Hg. The
15 residue is taken up in 300 ml of 2N NH₄OH and extracted 3 times with dichloromethane. The presence of an insoluble material is noted, this material being taken up twice in 20 ml of a 50/50 v/v MeOH/CH₂Cl₂ mixture. The organic phases are combined and washed with H₂O. After drying over Na₂SO₄ and concentration under vacuum, the black residue obtained is crystallized from 10 ml of CH₂Cl₂. The product is obtained as follows

20 Weight 1.2 g Yield = 60%

TLC CH₂Cl₂/MeOH 90/10 R_f = 0.50

NMR. DMSO ¹H δ (ppm) 4.82 (s, 2H), 6.97-7.12 (m, 6H), 7.80 (d, 1H), 8.1 (s, 1H), 11.75 (br, 1H)

Step 3-6 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

25 1.4 g (5.05 mmol) of compound of Step 2-6 and 35 ml of H₂O are introduced into a 100 ml one-necked flask fitted with a reflux condenser, followed by cautious addition of 35 ml of H₂SO₄. The suspension is maintained at reflux with stirring for 3 hours. After cooling, the beige-coloured precipitate is filtered off and washed to neutrality with H₂O and then with methanol

30 Weight: 1.5 g Yield = 100%

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.10$

m.p. = 360°C

Preparation C. 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline
-6-carboxylic acid

5 **Step 1 Methyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline**
 -6-carboxylate

11.8 g (38.0 mmol) of Preparation B, 120 ml of dimethylformamide and 7.9 g (57 mmol) of K_2CO_3 are introduced into a 250 ml three-necked flask. The suspension is stirred for 15 minutes at room temperature. 27 g (12 ml, 190 mmol) of iodomethane are added over 2
10 minutes. The suspension is stirred at room temperature for 30 to 45 minutes. The solvent is removed under vacuum and the residue is taken up in 500 ml of dichloromethane and washed with 3 times 300 ml of water. The organic phase is dried and the solvent is removed. The product is obtained as follows:

Weight 12 g Yield = 97.4%

15 TLC $\text{CH}_2\text{Cl}_2/\text{acetone}$ 98/2 $R_f = 0.60$

m.p. = 179.3°C

NMR (DMSO) ^1H δ (ppm): 3.6 (s, 3H), 3.90 (s, 3H), 5.1 (s, 2H); 7.2-7.4 (m, 5H), 7.55 (d, 1H), 8.25 (d, 1H); 8.6 (s, 1H)

20 **Step 2 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic**
 acid

The product is obtained with a yield of 100% (10 g) according to the procedure of Step 2-4 of Preparation B using 9.5 g (29.3 mmol) of compound obtained in Step 1.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.50$

m.p. = 227.2°C

25 NMR (DMSO) ^1H δ (ppm): 3.55 (s, 3H), 5.15 (s, 2H), 7.2-7.4 (m, 5H), 7.55 (d, 1H), 8.25 (d, 1H), 8.6 (s, 1H); 13.2 (bs, 1H)

Preparation D. 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-
6-carboxylic acid

Step 1 Methyl 3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

5.5 g (26.3 mmol) of compound of the Preparation A and 50 ml of pyridine are introduced into a round-bottomed flask. 5.0 g (33.1 mmol) of 3-fluorobenzyl isocyanate are added.

- 5 The mixture is maintained at reflux for 6 hours and 0.8 g (5.3 mmol) of 3-fluorobenzyl isocyanate is added in one portion. The mixture is heated overnight at reflux. The mixture is cooled and the product is precipitated with the addition of water and filtered. The product is reslurried in hot ethanol and filtered to provide 6.7 g (yield 78%) of the desired compound.

10 MS m/z (APCI, AP+) 329.1 [M]⁺

CHN Analysis Calcd (%) C, 62.20; H, 3.99, N, 8.53

Found (%) C, 62.09; H, 3.85, N, 8.42

Step 2 Methyl 1-methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

- 15 1.8 g (5.5 mmol) of the product from the preceding Step 1 is dissolved in 30 ml of dimethylformamide and 1.8 g (8.1 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding iodomethane 1.1 g (8.1 mmol). Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO₄. Slurried solid product in hot ethyl acetate and filtered to obtain 1.7 g (yield 90%) of the desired compound.

20 MS m/z (APCI, AP+) 343.1 [M]⁺

CHN Analysis Calcd (%) C, 63.16, H, 4.42, N, 8.18

Found (%) C, 63.02, H, 4.26, N, 8.06

- 25 **Step 3 1-Methyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

0.71 g of the compound (yield 76%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 2.

MS m/z (APCI, AP+) 329.0 [M]⁺

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CHN Analysis Calcd (%) C, 62.20, H, 3.99, N, 8.53
 Found (%) C, 61.94, H, 3.78, N, 8.57

Preparation E. 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

5

Step 1 Methyl 1-ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

2.0 g (6.1 mmol) of the compound of Step 1 of Preparation D are dissolved in 30 ml of dimethylformamide and 1.96 g (9.2 mmol) of cesium carbonate is added. The mixture is stirred 10 minutes before adding 1.4 g (9.2 mmol) of iodoethane. Stirring is continued overnight at room temperature. Water (60 ml) is added and the product is extracted with ethyl acetate (2 x 30 ml). The organic extracts are combined and washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO₄. Slurred solid product in hot ethyl acetate and filtered to obtain 1.4 g (yield 67%) of the desired compound.

15 MS m/z (APCI, AP+) 357.1 [M]⁺

CHN Analysis Calcd (%) C, 64.04, H, 4.81, N, 7.86
 Found (%) C, 63.72, H, 4.68, N, 7.75

Step 2 1-Ethyl-3-(3-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

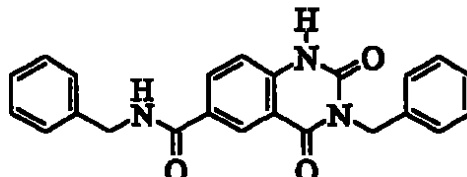
20 1.1 g of the compound (yield 71%) is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the preceding Step 1

MS m/z (APCI, AP+) 343.0 [M]⁺

CHN Analysis Calcd (%) C, 63.16, H, 4.42, N, 8.18
 Found (%) C, 63.06, H, 4.41, N, 8.03

25 Examples 1 to 461 illustrate, without limiting it, the synthesis of particularly active compounds of formula (I) according to the invention

Example 1 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide



0.150 g (0.51 mmol) of compound of Preparation B and 80 ml of anhydrous dimethylformamide are introduced into a stirred 25 ml one-necked flask protected from moisture. 0.054 g (56 μ l, 0.51 mmol) of benzylamine and 0.17 g (0.51 mmol) of TOTU are added to this solution. The solution is cooled in a bath to 0°C. 0.132 g (0.18 ml, 1.02 mmol) of N,N-diisopropylethylamine is then added. The mixture is warmed to room temperature and stirred overnight. After monitoring by TLC (90/10 CH₂Cl₂/MeOH), the DMF is removed under vacuum. The crystalline residue obtained is taken up in dichloromethane with the amount of methanol required for total dissolution. The organic phase is washed successively with 40 ml of 1N HCl, 40 ml of H₂O, 40 ml of saturated NaHCO₃ solution and finally 40 ml of H₂O. The organic phase is dried over Na₂SO₄ and the solvents are removed under vacuum. 0.140 g of product is obtained, which is recrystallized from 30 ml of acetonitrile.

Weight: 0.110 g Yield = 56%

TLC CH₂Cl₂/MeOH 90/10 R_f = 0.65

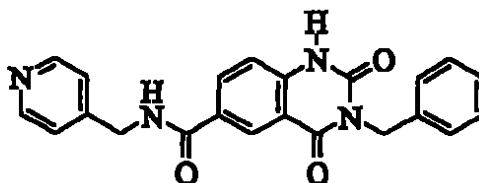
NMR. DMSO ¹H δ (ppm) 4.45 (d, 2H), 5.1 (s, 2H), 7.1-7.4 (m, 11H), 8.1 (d, 1H), 8.5 (s, 1H), 9.15 (m, 1H), 11.75 (bs, 1H)

IR. 3425, 2364, 1722, 1640, 1509, 1442, 1304, 1261, 1078, 927, 845 cm⁻¹

m.p. = 241.2°C

HPLC 98.3%

Example 2 . 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide



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The product is obtained with a yield of 46% (0.090 g) according to the procedure of Example 1 using 4-picolylamine, and after recrystallization from a 50/50 EtOAc/EtOH mixture.

TLC CH₂Cl₂/MeOH 90/10 R_f = 0.60

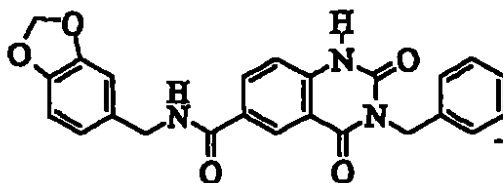
5 NMR. DMSO ¹H δ (ppm) 4.5 (d, 2H), 5.1 (s, 2H), 7.2-7.4 (m, 8H), 8.15 (d, 1H), 8.5 (d, 2H), 8.55 (s, 1H), 9.25 (t, 1H), 11.75 (s, 1H)

IR 3250, 1725, 1669, 1642, 1623, 1450, 1345, 1301, 1075, 1006, 830 cm⁻¹

m.p. = 305.2°C

HPLC 95.1%

10 **Example 3 : 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**



The product is obtained with a yield of 64% (0.140 g) according to the procedure of Example 1 using piperonylamine, and after crystallization from acetonitrile

15 TLC CH₂Cl₂/MeOH 90/10 R_f = 0.65

NMR. DMSO ¹H δ (ppm) 4.35 (d, 2H), 5.1 (s, 2H), 5.95 (s, 2H), 6.7-6.95 (m, 3H), 7.15-7.4 (m, 6H), 8.15 (d, 1H), 8.5 (s, 1H), 9.1 (t, 1H), 11.7 (bs, 1H)

IR 3200, 1727, 1636, 1493, 1444, 1299, 1261, 1041, 938, 841, 763, 726 cm⁻¹

m.p. = 256°C

20 HPLC 99%

Example 4 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-thienylmethyl)amide

The product is obtained with a yield of 40% (0.080 g) according to the procedure of Example 1, but using 2-thienylmethylamine, and after a crystallization from acetonitrile.

25 TLC CH₂Cl₂/MeOH 90/10 R_f = 0.65

NMR. DMSO ^1H δ (ppm) 4.35 (d,2H), 4.85 (s,2H), 6.7-6.85 (m,2H), 6.95-7.2 (m,7H), 7.9 (d,1H), 8.3 (s,1H), 9.05 (t,1H), 11.55 (bs,1H)

IR. 1729,1637,1511,1444,1346,1298,1261,1072,845,763 cm^{-1}

m.p. = 236.3°C

5 HPLC 98.7%

Example 5 · 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (3-pyridylmethyl)amide

10 The product is obtained with a yield of 66% (0.130 g) according to the procedure of Example 1, but using 3-(aminomethyl)-pyridine, and after a crystallization from acetonitrile.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 R_f = 0.40

NMR DMSO ^1H δ (ppm) 4.5 (d,2H), 5.15 (s,2H), 7.15-7.4 (m,7H), 7.7 (d,1H), 8.15 (d,1H), 8.45 (d,1H), 8.55 (d,2H), 9.25 (t,1H), 11.8 (s,1H)

15 IR. 3345,1716,1670,1638,1621,1450,1433,1348,1298,1068,829,774 cm^{-1}

m.p. = 252.3°C

HPLC 97.4%

Example 6 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

20

The product is obtained with a yield of 47.2% (0.100 g) according to the procedure of Example 1, but using 4-methoxybenzylamine, and after a crystallization from acetonitrile.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 R_f = 0.45

25 NMR DMSO ^1H δ (ppm) 3.7 (s,3H), 4.4 (d,2H), 5.1 (s,2H), 6.9 (d,2H), 7.2-7.4 (m,8H), 8.15 (d,1H), 8.5 (s,1H), 9.15 (t,1H), 11.8 (bs,1H)

IR. 3400,3210,1727,1638,1513,1441,1300,1253,1173,1040,843, 760 cm^{-1}

m.p. = 269°C

HPLC 100%

Example 7 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-chlorobenzylamide

5 The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-chlorobenzylamine, and after a crystallization from acetonitrile.
TLC CH₂Cl₂/MeOH 95/5 R_f = 0.45
NMR. DMSO ¹H δ (ppm) 4.5 (d, 2H), 5.1 (s, 2H), 7.2-7.45 (m, 10 H); 8.15 (d, 1H), 8.5 (s, 1H), 9.25 (t, 1H), 11.8 (bs, 1H)
10 IR. 3365, 3200, 1726, 1638, 1551, 1512, 1444, 1305, 1263, 1012, 844, 763 cm⁻¹
m.p. = 280.6°C
HPLC 98.1%

Example 8 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methylbenzylamide

15 The product is obtained with a yield of 19% (0.040 g) according to the procedure of Example 1, but using 4-methylbenzylamine, and after a crystallization from acetonitrile.
TLC CH₂Cl₂/MeOH 95/5 R_f = 0.40
NMR. DMSO ¹H δ (ppm) 2.3 (s, 3H), 4.4 (d, 2H), 5.1 (s, 2H), 7.0-7.4 (m, 10H), 8.15 (d, 1H), 8.55 (s, 1H), 9.1 (t, 1H), 11.8 (bs, 1H)
20 IR. 3280, 1720, 1671, 1640, 1623, 1550, 1278, 848, 774, 744 cm⁻¹
m.p. = 267.8°C
HPLC 98.7%

Example 9 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

25
0.500 g (1.61 mmol) of compound of Preparation C in 25 ml of anhydrous dimethylformamide are introduced into a stirred 50 ml one-necked flask protected from moisture. 0.244 g (0.201 ml, 1.61 mmol) of piperonylamine and 0.531 g (1.61 mmol) of TOTU are added to this solution. The solution is cooled in a cold bath to 0°C. 0.415 g

30

(0.564 ml, 3.22 mmol) of *N,N*-diisopropylethylamine is then added. The mixture is warmed to room temperature and stirred overnight.

After monitoring by TLC (90/10 CH₂Cl₂/MeOH), DMF is removed under vacuum. The crystalline residue obtained is taken up in dichloromethane. The organic phase is washed successively with 1N HCl, H₂O, saturated NaHCO₃ and finally H₂O. The organic phase is dried over Na₂SO₄ and the solvent is removed under vacuum. 0.540 g of product, recrystallized from 30 ml of acetonitrile, is obtained as follows

Weight: 0.390 g Yield = 54.6%

TLC CH₂Cl₂/acetone 90/10 R_f = 0.40

NMR. DMSO ¹H δ (ppm) 3.55 (s, 3H), 4.35 (d, 2H), 5.15 (s, 2H), 6.0 (s, 2H), 6.75-6.95 (m, 3H), 7.2-7.4 (m, 5H), 7.55 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H)

IR. 3303, 1703, 1656, 1637, 1498, 1444, 1322, 1254, 1040, 932, 845 cm⁻¹

m.p. = 215 °C

HPLC 99.5%

Example 10. 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

The product is obtained with a yield of 56.8% (0.110 g) according to the procedure of Example 9, but using benzylamine, and after a crystallization from acetonitrile.

TLC CH₂Cl₂/acetone 90/10 R_f = 0.55

NMR. CDCl₃ ¹H δ (ppm) 3.65 (s, 3H), 4.65 (d, 2H), 5.3 (s, 2H), 6.55 (m, 1H), 7.2-7.6 (m, 11H), 8.3 (d, 1H), 8.5 (s, 1H),

IR. 1708, 1655, 1641, 1616, 1507, 1478, 1326, 1246, 930, 750 cm⁻¹

m.p. = 198.9 °C

HPLC 100%

Example 11 Methyl 4-([1-(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl)methanoyl]amino)methyl)benzoate

The product is obtained with a yield of 61.5% (0.135 g) according to the procedure of Example 9, but using methyl 4-(aminomethyl)benzoate hydrochloride and 3.5 equivalents

of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH₂Cl₂/MeOH gradient, followed by a solidification in ether

TLC CH₂Cl₂/MeOH 95/5 R_f = 0.36

NMR. DMSO ¹H δ (ppm) 3.55 (s,3H), 3.85 (s,3H), 4.55 (d,2H), 5.15 (s,2H), 7.2-7.35 (m,5H), 7.45 (d,2H), 7.6 (d,1H), 7.95 (d,2H), 8.3 (d,1H), 8.65 (s,1H), 9.35 (t,1H)

IR. 1723, 1706, 1657, 1642, 1617, 1506, 1477, 1284, 1109, 749 cm⁻¹

m.p. = 196°C

HPLC 100%

Example 12. 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide

The product is obtained with a yield of 42% (0.090 g) according to the procedure of Example 9, but using 4-hydroxy-3-methoxybenzylamine hydrochloride and 3.5 equivalents of N,N-diisopropylethylamine. The crude product is purified by chromatography on silica, using a 95/5 CH₂Cl₂/MeOH gradient, followed by a solidification in ether

TLC CH₂Cl₂/MeOH 95/5 R_f = 0.59

NMR. DMSO ¹H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 4.4 (d,2H), 5.15 (s,2H), 6.75 (s,2H), 6.95 (s,1H), 7.2-7.40 (m,6H), 7.55 (d,1H), 8.3 (d,1H), 8.65 (s,1H), 8.8 (s,1H), 9.15 (t,1H)

IR. 1707, 1655, 1618, 1502, 1477, 1277, 704 cm⁻¹

m.p. = 183°C

HPLC. 87.1%

Example 13 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

The product is obtained with a yield of 77.7% (0.320 g) according to the procedure of Example 9, but using 4-methoxybenzylamine. The crude product is purified by chromatography on silica, using 97/3 CH₂Cl₂/MeOH as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off

TLC CH₂Cl₂/MeOH 90/10 R_f = 0.8

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.75 (s,3H); 4.45 (d,2H), 5.2 (s,2H), 6.9 (d,2H), 7.2-7.4 (m,7H), 7.6 (d,1H), 8.3 (d,1H), 8.65 (s,1H), 9.25 (t,1H)

IR. 1705,1660,1636,1505,1251,750 cm^{-1}

m.p. = 191°C

5 HPLC: 97.3%

Example 14 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl)amide

10 The product is obtained with a yield of 67.7% (0.130 g) according to the procedure of Example 9, but using 4-picolylamine.

The crude product is purified by chromatography on silica, using 95/5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ as eluent. The desired fractions are combined and concentrated. The product is solidified in ether and then filtered off.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 R_f = 0.18

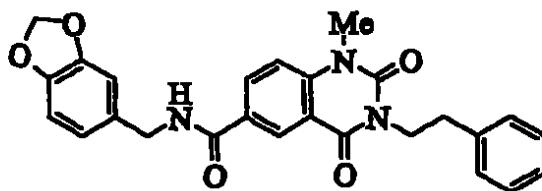
15 NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 4.55 (d,2H), 5.15 (s,2H), 7.2-7.4 (m,7H), 7.6 (d,1H), 8.3 (d,1H), 8.5 (d,2H), 8.65 (s,1H), 9.35 (t,1H)

IR. 1705,1658,1634,1508,1332,831,749,705 cm^{-1}

m.p. = 172°C

HPLC: 98.8%

20 **Example 15 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**



Step 1 Methyl 2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate

25 0.750 g (3.6 mmol) of compound of Preparation A and 7.5 ml of pyridine are introduced into a round-bottomed flask. 0.530 g (0.5 ml, 3.6 mmol) of phenethyl isocyanate is added.

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The mixture is maintained at 100°C overnight. Since the reaction is incomplete, a second addition of phenethyl isocyanate, i.e. 2 equivalents, is carried out. After precipitation with H₂O, filtration and purification by reslurrying in hot ethanol, the product is obtained as follows

5 Weight: 0.640 g Yield = 54.9%

NMR. DMSO ¹H δ (ppm) 2.85-2.95 (m, 2H), 4.90 (s, 3H), 4.05-4.15 (m, 2H), 7.15-7.3 (m, 6H), 8.15 (d, 1H), 8.45 (s, 1H), 11.8 (bs, 1H)

Step 2 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

10 The product from the preceding step is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.500 g of the desired compound (yield 80%)

NMR. DMSO ¹H δ (ppm) 2.85-2.95 (m, 2H), 4.05-4.15 (m, 2H), 7.15-7.3 (m, 6H), 8.15 (d, 1H), 8.45 (s, 1H), 11.75 (s, 1H), 13.05 (bs, 1H)

Step 3 2,4-Dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

15 The product is obtained with a yield of 57.8% (0.205g) according to the procedure of Example 1, using 250 mg (0.8 mmol) of the compound obtained in the preceding Step 2 and piperonylamine.

NMR. DMSO ¹H δ (ppm) 2.9 (t, 2H), 4.1 (t, 2H), 4.4 (d, 2H), 5.95 (s, 2H), 6.75-6.95 (m, 3H), 7.15-7.35 (m, 6H), 8.1 (d, 1H), 8.5 (s, 1H), 9.1 (t, 1H), 11.65 (bs, 1H)

20 IR. 3249, 1704, 1658, 1636, 1488, 1251, 810, 753 cm⁻¹

m.p. = 296°C

HPLC 99.5%

Step 4. 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

25 0.190 g (0.46 mmol) of the product from the preceding Step 3, 2 ml of dimethylformamide and 0.095 g (0.68 mmol) of K₂CO₃ are introduced into a 25 ml round-bottomed flask. The mixture is stirred for 15 min at room temperature and 0.325 g (0.15 ml, 2.29 mmol) of iodomethane is then added. Stirring is continued for 30 to 45 minutes. The solvent is

removed under vacuum. The residue is taken up in dichloromethane and washed with H₂O. The organic phase is separated out after settling and dried over Na₂SO₄. After concentration under vacuum, the product is purified by chromatography on silica, using a 98/2 CH₂Cl₂/MeOH gradient, and then solidified in ether to provide 0.080g of the desired compound (yield 76%)

NMR. DMSO-¹H δ (ppm) 2.9 (t,2H), 3.55 (s,3H), 4.15 (t,2H), 4.4 (d,2H), 5.95 (s,2H), 6.8-6.95 (m,3H), 7.15-7.35 (m,5H), 7.55 (d,1H), 8.25 (d,1H), 8.6 (s,1H), 9.15 (t,1H)

IR. 3272,1705,1664,1635,1501,1254,1041,751,698 cm⁻¹

m.p. = 183°C

HPLC: 99.7%

Example 16 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

Step 1 Methyl 3-(4-methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The product is obtained with a yield of 61.3% (0.750g) according to the procedure of Step 1 of Example 15, but using 4-methoxybenzyl isocyanate

NMR. DMSO-¹H δ (ppm) 3.7 (s,3H), 3.8 (s,3H), 5.0 (s,2H), 6.8-6.85 (m,2H), 7.2-7.3 (m,3H), 8.1-8.2 (m,1H), 8.5 (s,1H), 11.9 (bs,1H)

Step 2 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product from the preceding Step 1 is hydrolysed to the acid according to the procedure of Step 2-4 of Preparation B to provide 0.680 g of the desired compound (yield 94.8%)

NMR. DMSO-¹H δ (ppm) 3.7 (s,3H), 5.0 (s,2H), 6.8-7.9 (m,2H), 7.2-7.3 (m,3H), 8.1-8.2 (m,1H), 8.5 (s,1H), 11.8 (s,1H), 13.1 (bs,1H)

Step 3 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 79.9% (0.220g) according to the procedure of Example 9, using 200 mg (0.6 mmol) of the compound obtained in the preceding Step 2 and piperonylamine. The crude product is solidified in dichloromethane.

5 NMR. DMSO ^1H δ (ppm) 3.7 (s, 3H), 4.35 (d, 2H), 5.0 (s, 2H), 5.95 (s, 2H), 6.75-6.9 (m, 5H), 7.2-7.3 (m, 3H), 8.1 (d, 1H), 8.5 (s, 1H); 9.1 (t, 1H), 11.75 (s, 1H)
IR. 1720, 1648, 1634, 1504, 1442, 1300, 1250, 1036, 766 cm^{-1}
m.p. = 252°C
HPLC 96.2%

10 **Example 17: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The alkylation with methyl iodide of the product obtained in Example 16 is carried out using the procedure described in Example 15, Step 4. After crystallization from ether, 0.080 g of the product is obtained (yield 70.4%) -

15 NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.7 (s, 3H), 4.4 (d, 2H), 5.05 (s, 2H), 5.95 (s, 2H), 6.8-6.95 (m, 5H), 7.3 (d, 2H), 7.55 (d, 1H), 8.25 (d, 1H), 8.6 (s, 1H), 9.2 (t, 1H)
IR. 3265, 1704, 1662, 1634, 1504, 1443, 1320, 1248, 1040, 771 cm^{-1}
m.p. = 178°C
HPLC 99.2%

20 **Example 18: 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide**

Step 1 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-methoxybenzyl)amide

25 The product is obtained with a yield of 82% (0.270g) according to the procedure of Example 9, using 240 mg (0.74 mmol) of the compound obtained in Step 2 of Example 16 and 4-methoxybenzylamine

NMR. DMSO ^1H δ (ppm) 3.7 (2s, 6H), 4.4 (d, 2H), 5.0 (s, 2H), 6.8-6.95 (m, 4H), 7.2-7.35 (m, 5H), 8.15 (d, 2H), 8.5 (s, 1H), 9.15 (t, 1H), 11.75 (bs, 1H)

Step 2. 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide

The product is obtained with a yield of 94.4% (0.260g) according to the procedure of Example 15 Step 4, using the compound obtained in the preceding in Step 1

5 NMR. DMSO ^1H δ (ppm) 3.6 (s,3H), 3.7 (dd,6H), 4.45 (d,2H), 5.1 (s,2H), 6.8-6.95 (m,4H); 7.25-7.40 (m,4H), 7.55 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.2 (t,1H)

IR. 1705,1655,1641,1614,1510,1247,1175,1033 cm^{-1}

m.p. = 195°C

HPLC 99.5%

10 **Example 19: 3-(1-Naphth-1-ylethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained according to the procedure of Example 16, Step 1 to 3, using 1-(1-naphthyl)ethyl isocyanate in the Step 1

15 NMR. DMSO ^1H δ (ppm) 1.95 (d,3H), 4.35 (d,2H), 6.0 (s,2H), 6.7-6.8 (m,2H), 6.8-6.9 (m,2H), 7.2 (d,1H), 7.4-7.5 (m,2H), 7.6 (t,1H), 7.85-8.0 (m,5H), 8.10 (d,1H), 8.45 (s,1H); 9.10 (t,1H), 11.6 (bs,1H)

Example 20: 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

20 **Step 1: Dimethyl 4-(3-pyrid-4-ylmethylareido)isophthalate**

The product is obtained with a yield of 94.2% according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 4-pyridine methylamine.

25 NMR. DMSO ^1H δ (ppm) 3.8 (s,3H), 3.9 (s,3H), 4.3 (d,2H), 7.30-7.35 (m,2H); 8.0-8.1 (m,1H), 8.4 (t,1H), 8.5-8.6 (m,4H), 10.3 (s,1H)

Step 2 Methyl 2,4-dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-

carboxylate

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the compound obtained in the preceding Step 1

5 NMR. DMSO ^1H δ (ppm) 3.85 (s,3H), 5.1 (s,2H), 7.20-7.30 (m,3H), 8.2 (d,1H), 8.4-8.5 (m,3H), 11.95 (bs,1H)

Step 3 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

The product is obtained according to the procedure of Step 2-4 of Preparation B, using the compound obtained in the preceding Step 2

10 NMR. DMSO ^1H δ (ppm) 5.1 (s,2H), 7.20-7.30 (m,3H), 8.2 (d,1H), 8.4-8.5 (m,3H), 11.9 (s,1H), 13.1 (bs,1H)

Step 4 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

15 The product is obtained with a yield of 26.7% (0.850 g) according to the procedure of Example 1, using the compound obtained in the preceding Step 3 and piperonylamine. After filtering off an insoluble material, the dimethylformamide is removed under vacuum. The residue is solidified in dichloromethane.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 R_f = 0.40

20 NMR. DMSO ^1H δ (ppm) 4.40 (d,2H), 5.0 (s,2H), 5.95 (s,2H), 6.80-6.9 (m,3H), 7.20-7.30 (m,3H), 8.1-8.2 (m,1H), 8.4-8.5 (m,3H), 9.1 (t,1H), 11.8 (s,1H)

IR. 3267,1713,1645,1626,1444,1313,1040,920,769 cm^{-1}

m.p. = 291.2°C

HPLC 87.7%

Example 21: 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

25

Step 1 Methyl N-benzyl-6-(3-thien-2-ylmethylureido)isophthalate

The product is obtained according to the procedure of Step 1-5 of Preparation B, using the compound obtained in the Preparation A and 2-thiophene methylamine.

NMR. DMSO ^1H δ (ppm) 3.8 (s,3H), 3.9 (s,3H), 4.5 (d,2H), 6.9-7.0 (m,2H), 7.4 (m,1H),
5 8.0-8.05 (m,1H), 8.4 (t,1H), 8.5 (s,1H), 8.6-8.65 (m,1H), 10.15 (s,1H)

Step 2 Methyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The product is obtained according to the procedure of Step 2-5 of Preparation B, using the
10 compound obtained in the preceding Step 1

NMR. DMSO ^1H δ (ppm) 3.8 (s,3H), 5.25 (s,2H), 6.9 (d,1H), 7.1 (s,1H), 7.25 (d,1H), 7.4
(d,1H), 8.1-8.15 (m,1H), 8.5 (s,1H), 11.9 (bs,1H)

Step 3 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

15 The product is obtained according to the procedure of Step 2-4 of Preparation B, using the compound obtained in the preceding Step 2.

NMR. DMSO ^1H δ (ppm) 5.25 (s,2H), 6.95 (d,1H), 7.15 (d,1H), 7.2-7.3 (m,1H), 7.4
(d,1H), 8.1-8.2 (m,1H), 8.5 (s,1H), 11.9 (s,1H), 13.1 (bs,1H)

Step 4 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide

20

The product is obtained with a yield of 61.9% (0.160 g) according to the procedure of Example 1, using the compound obtained in the preceding Step 3 and benzylamine.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 R_f = 0.8

25 NMR. DMSO ^1H δ (ppm) 4.50 (d,2H), 5.2 (s,2H), 6.90-7.4 (m,9H), 8.15 (d,1H), 8.6
(s,1H), 9.2 (t,1H), 11.8 (s,1H)

IR 3185,1730,1646,1633,1512,1446,1292,1260,845,763 cm^{-1}

m.p = 264.8°C

HPLC 99.5%

**Example 22 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline
-6-carboxylic acid benzylamide**

The product is obtained with a yield of 87% (0.090 g) according to the procedure of Step 4
of Example 15, using the compound obtained in the Example 21

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 $R_f = 0.8$

NMR. DMSO ^1H δ (ppm) 3.6 (s, 3H), 4.50 (d, 2H), 5.3 (s, 2H), 6.90-7.0 (m, 1H), 7.2-7.5
(m, 7H), 7.55 (d, 1H), 8.3 (d, 1H), 8.7 (s, 1H), 9.25 (t, 1H)

IR. 3257, 1704, 1657, 1637, 1513, 1480, 1325, 1251, 829, 787 cm^{-1}

m.p. = 223 $^{\circ}\text{C}$

HPLC 99.9%

**Example 23 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 59% (0.170 g) according to the procedure of
Example 1, using the compound obtained in Step 3 of Example 21 and piperonylamine.

The crude product is solidified in dichloromethane

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 $R_f = 0.4$

NMR. DMSO ^1H δ (ppm) 4.40 (d, 2H), 5.25 (s, 2H), 6.0 (s, 2H), 6.75-7.0 (m, 4H), 7.1
(s, 1H), 7.25 (d, 1H), 7.40 (d, 1H), 8.2 (d, 1H), 8.55 (s, 1H), 9.20 (t, 1H), 11.8 (s, 1H)

IR. 3185, 1727, 1632, 1502, 1445, 1300, 1259, 1040, 936, 846, 765 cm^{-1}

m.p. = 270.1 $^{\circ}\text{C}$

HPLC. 95.2%

**Example 24 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 79.7% (0.085 g) according to the procedure of Step
4 of Example 15, using the compound obtained in the Example 23

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 $R_f = 0.8$

NMR. DMSO ^1H δ (ppm) 3.6 (s,3H), 4.40 (d,2H), 5.30 (s,2H), 6.0 (s,2H), 6.8-7.0 (m,4H), 7.2 (d,1H); 7.40 (d,1H), 7.5-7.6 (m,1H), 8.2-8.30 (m,1H), 8.6 (s,1H), 9.20 (t,1H)

IR. 3251,1705,1659,1635,1501,1446,1328,1253,1041,926,784 cm^{-1}

m.p. = 224.2°C

5 HPLC 99.8%

Example 25 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

10 The product is obtained with a yield of 67.8% (0.170 g) according to the procedure of Example 15 Steps 1 to 3, using in the first step the compound obtained in the Preparation A and 4-chlorobenzyl isocyanate. The product is obtained after solidification in dichloromethane.

15 NMR. DMSO ^1H δ (ppm) 4.35 (t,2H), 5.1 (s,2H), 5.95 (s,2H), 6.75-6.9 (m,3H); 7.25 (d,1H), 7.35 (s,4H), 8.15 (d,1H), 8.5 (s,1H), 9.15 (t,1H), 11.8 (bs,1H)

IR. 3265,1734,1653,1633,1504,1440,1254,1041,811,761 cm^{-1}

m.p. = 290°C

HPLC 99.2%

20 **Example 26 3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 88.9% (0.085 g) according to the procedure of Example 15 Step 4, using the compound obtained in Example 25. The product is isolated after crystallization in ether.

25 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 4.40 (t,2H), 5.15 (s,2H), 5.95 (s,2H), 6.75-6.9 (m,3H), 7.35 (s,4H), 7.55 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

IR. 3249,1704,1658,1636,1488,1251,810,753 cm^{-1}

m.p. = 231°C

HPLC 99.6%

**Example 27 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
(benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained (0.035 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and monomethylamine, and in Step 4, piperonylamine for the amidation.

TLC CH₂Cl₂/MeOH 90/10 R_f = 0.50

NMR. DMSO ¹H δ (ppm) 3.35 (s, 3H), 3.55 (s, 3H), 4.40 (d, 2H), 6.0 (s, 2H), 6.75-6.95 (m, 3H), 7.55 (d, 1H), 8.25 (d, 1H), 8.6 (s, 1H); 9.25 (t, 1H)

IR. 1703, 1649, 1501, 1486, 1256, 1037, 923 cm⁻¹

m.p. = 279°C

HPLC 97.3%

**Example 28 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline
-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

The product is obtained with a yield of 36% (0.040 g) according to the procedure of Example 20 Steps 1 to 4, using in the first step the compound obtained in the Preparation A and piperonylamine, and in Step 4, piperonylamine for the amidation.

Step 1 Dimethyl 4-(3-benzo[1,3]dioxol-5-ylmethylureido)isophthalate

NMR. CDCl₃ ¹H δ (ppm) 3.9 (s, 6H), 4.4 (s, 2H), 5.1 (t, 1H), 6.70-6.85 (m, 3H), 6.95 (s, 2H), 8.1-8.2 (m, 1H), 8.6-8.7 (m, 2H), 10.6 (bs, 1H)

**Step 2 Methyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-
tetrahydroquinazoline-6-carboxylate**

NMR. DMSO ¹H δ (ppm) 3.8 (s, 3H), 5.0 (s, 2H); 5.9 (s, 2H), 6.8 (s, 2H), 6.9 (s, 1H), 7.25 (d, 1H), 8.15 (d, 1H), 8.5 (s, 1H), 11.8 (bs, 1H)

**Step 3 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-
tetrahydroquinazoline-6-carboxylic acid**

NMR. DMSO ^1H δ (ppm) 5.0 (s, 2H), 6.0 (s, 2H), 6.8 (s, 2H), 6.9 (s, 1H), 7.3 (d, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 11.85 (s, 1H), 13.05 (bs, 1H)

Step 4 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

5 TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5

R_f = 0.70

NMR. DMSO ^1H δ (ppm) 4.40 (s, 2H), 5.0 (s, 2H), 5.9 (s, 4H), 6.75-6.95 (m, 6H), 7.20-7.30 (m, 1H), 8.05-8.15 (m, 1H), 8.45-8.55 (m, 1H), 9.1 (m, 1H), 10.3 (m, 1H)

IR. 3271, 1739, 1649, 1630, 1503, 1440, 1250, 1041, 926, 759 cm^{-1}

10 m.p. = 245.2°C

HPLC 81.5%

Example 29. 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

15 The product is obtained with a yield of 40.5% (0.050 g) according to the procedure of Example 15 Step 4, using the compound obtained in the Example 28

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 R_f = 0.80

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 4.35 (s, 2H), 5.0 (s, 2H), 6.0 (s, 4H), 6.80-7.0 (m, 6H), 7.5 (d, 1H), 8.25 (d, 1H), 8.6 (s, 1H), 9.15-9.2 (m, 1H)

20 IR. 3302, 1703, 1663, 1630, 1490, 1247, 1041, 929, 807, 785 cm^{-1}

m.p. = 197.5°C

HPLC 100%

Example 30. 3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

25 0.150 g (0.35 mmol) of compound of Example 2, and then 3 ml of anhydrous DMF are introduced into a stirred round-bottomed flask protected from moisture. 0.075 g

(0.525 mmol) of K_2CO_3 is added to the stirred solution. The mixture is stirred for 15 minutes and 0.273 g (0.14 ml, 1.75 mmol) of iodoethane is then added. Stirring is continued for about 1 hour. After removing the solvent under vacuum, the residue is dissolved in 50 ml of dichloromethane and washed with 2x 50 ml of H_2O . After drying over Na_2SO_4 and concentration under vacuum, the product is crystallized from 8 ml of acetonitrile. The product is obtained as follows

Weight: 0.070 g Yield = 43.7%

TLC $CH_2Cl_2/MeOH$ 95/5 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 1.25 (t, 3H), 4.2 (q, 2H), 4.4 (d, 2H), 5.15 (s, 2H), 5.95 (s, 2H); 6.75-6.95 (m, 3H), 7.2-7.4 (m, 5H), 7.65 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.15 (t, 1H)

IR. 1701, 1658, 1633, 1506, 1488, 1458, 1246, 1217, 1038, 926, 803 cm^{-1}

m.p. = 176 $^{\circ}C$

HPLC 99%

Example 31. 3-Benzyl-1-cyclopropylmethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 76.8% (0.130 g) according to the procedure of Example 30, using cyclopropylmethyl bromide. The product is obtained after solidification in diisopropyl ether

TLC $CH_2Cl_2/MeOH$ 95/5 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 0.4-0.55 (m, 4H), 1.25 (m, 1H), 4.1 (d, 2H), 4.35 (d, 2H), 5.15 (s, 2H), 5.95 (s, 2H), 6.85 (m, 3H), 7.3 (m, 5H), 7.7 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H)

IR. 1703, 1656, 1641, 1504, 1467, 1307, 1261, 1241, 1043, 936, 845, 748 cm^{-1}

m.p. = 184 $^{\circ}C$

HPLC 97.2%

Example 32: 3-Benzyl-1-isobutyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

The product is obtained with a yield of 35.3% (0.060 g) according to the procedure of Example 30, using isobutyl bromide.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 $R_f = 0.65$

NMR. CDCl_3 ^1H δ (ppm) 1.0 (d, 6H), 2.15 (m, 1H), 4.0 (d, 2H), 4.5 (d, 2H), 4.25 (s, 2H), 5.95 (s, 2H), 6.55 (m, 1H), 6.8 (m, 3H), 7.25 (m, 4H), 7.45 (d, 2H); 8.25 (t, 1H), 8.45 (s, 1H)

IR. 1705, 1660, 1643, 1548, 1502, 1456, 1303, 1260, 1245, 1043, 923 cm^{-1}

m.p. = 146 $^\circ\text{C}$

HPLC 96.8%

10 **Example 33: 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide**

15 **Step 1. Methyl 1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**
0.870 g (2.7 mmol) of compound obtained in Step 1 of Preparation C, 20 ml of benzene and 2.1 g (16.1 mmol) of AlCl_3 are maintained at 50 $^\circ\text{C}$ for 7 hours. After cooling, the medium is precipitated on a water/ice mixture. The insoluble material is dissolved in dichloromethane and purified by flash chromatography, eluting with a gradient of $\text{CH}_2\text{Cl}_2/\text{acetone}$. 0.510 g of the desired compound is obtained.

Step 2. 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

20 The saponification of the compound obtained in the preceding Step 1 is carried out with LiOH in a dioxane/ H_2O mixture as for the preceding examples. Amidation with piperonylamine gives 0.160 g of the desired product.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.45$

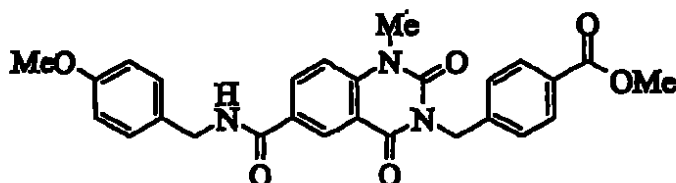
25 NMR. DMSO ^1H δ (ppm) 3.45 (s, 3H); 4.4 (d, 2H), 6.0 (s, 2H), 6.75-6.95 (m, 3H), 7.5 (d, 1H), 8.25 (d, 1H), 8.55 (s, 1H), 9.2 (t, 1H), 11.7 (s, 1H)

IR. 3290, 1697, 1635, 1503, 1484, 1324, 1258, 1040, 844 cm^{-1}

m.p. = 279 $^\circ\text{C}$

HPLC 98.7%

Example 34 Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate



**Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
4-methoxy-benzylamide**

Preparation identical to that of Example 33, using 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (NMR. DMSO ^1H δ (ppm) 3.50 (s, 3H), 7.5 (d, 1H), 8.20 (d, 1H), 8.50 (s, 1H), 11.75 (bs, 1H), 13.1 (bs, 1H)) and 4-methoxy-benzylamine in DMF with TOTU and DIPEA. The product is obtained as follows

NMR. DMSO ^1H δ (ppm) 3.50 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.50 (d, 1H), 8.20 (d, 1H), 8.55 (s, 1H), 9.20 (t, 1H), 11.65 (bs, 1H),

Step 2 Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

0.8 g (2.36 mmol) of the product obtained in the preceding Step 1 and 8 ml anhydrous DMF are stirred with 1.15 g (3.54 mmol) of cesium carbonate. Stirring is continued for 15 minutes and then 0.81 g (3.54 mmol) of methyl-4-(bromomethyl)benzoate is added. The mixture is maintained at 90°C for 1h15min and then stirred overnight. 15ml of water are added and then extracted with dichloromethane. The organic phase is washed with water and concentrated to dryness on a rotavapor. The product obtained is purified with flash chromatography eluting with a gradient of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to provide 0.220 g of the desired product.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.85$

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.7 (s, 3H), 3.85 (s, 3H), 4.4 (d, 2H), 5.25 (s, 2H), 6.9 (d, 2H), 7.25 (d, 2H), 7.45 (d, 2H), 7.55 (d, 1H), 7.9 (d, 2H), 8.25 (dd, 1H), 8.6 (s, 1H), 9.2 (t, 1H)

IR $\cdot$ 3387, 1709, 1658, 1642, 1508, 1286, 1248, 1110, 1032, 835, 750 cm^{-1}

m.p = 189.2 °C

HPLC . 96.5 %

Example 35: 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid

0.16 g (3.3 mmol) of the product obtained in Example 34 is hydrolysed in a mixture of 1.2 ml of dioxane and 4.2 ml of water with 28 mg of LiOH monohydrate. The mixture is maintained at reflux for 10 minutes to complete the reaction. After acidification at pH 1 with concentrated HCl, the precipitate is filtered off to provide 0.120 g of the desired compound

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.50

NMR. DMSO ¹H δ (ppm) 3.55 (s, 3H), 3.75 (s, 3H), 4.4 (d, 2H), 5.20 (s, 2H), 6.9 (d, 2H), 7.25 (d, 2H), 7.40 (d, 2H); 7.60 (d, 1H), 7.85 (d, 2H), 8.25 (dd, 1H), 8.65 (s, 1H), 9.2 (t, 1H) 12.9 (bs, 1H)

IR 3378, 1702, 1658, 1645, 1616, 1506, 1297, 1248, 1125, 839, 788, 751 cm⁻¹

m.p = 262.5 °C

HPLC . 100 %

Example 36: 1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide

0.100 g (0.28 mmol) of compound of Example 33 and 1 ml of anhydrous DMF are stirred with 0.060 g (0.42 mmol) of K₂CO₃. The mixture is maintained for 15 min, followed by addition of 0.085 g (0.42 mmol) of cinnamyl bromide. The mixture is maintained at 70°C for 2 hours. After concentration under vacuum, the residue is taken up in dichloromethane, washed with H₂O and then dried over Na₂SO₄. The solvent is removed and the product is purified by flash chromatography, eluting with a 95/5 gradient of CH₂Cl₂/MeOH. A solidification in ether provides 0.070 g (yield=51%) of the desired compound.

TLC CH₂Cl₂/MeOH 95/5 R_f = 0.46

NMR. DMSO ¹H δ (ppm) 3.55 (s, 3H), 4.4 (d, 2H), 4.75 (d, 2H), 6.0 (s, 2H), 6.3-6.4 (m, 1H), 6.6 (d, 1H), 6.80-6.95 (m, 3H), 7.2-7.35 (m, 3H), 7.4 (d, 2H), 7.55 (d, 1H), 8.25 (d, 1H); 8.65 (s, 1H), 9.25 (t, 1H)

IR. 1659, 1643, 1503, 1477, 1246, 754 cm⁻¹

m.p = 174°C

HPLC 98.4%

Example 37 Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

A mixture of 0.5 g (1.7 mmol) of the compound of Preparation B, 0.44 g (1.7 mmol) of triphenylphosphine and 0.44 ml (4.3 mmol) of benzyl alcohol is stirred in 20 ml of THF. A solution of 0.27 ml (1.7 mmol) of DEAD in 10 ml of THF is added dropwise with stirring. Stirring is continued overnight at room temperature. The precipitate formed is filtered through Celite and the filtrate is concentrated under vacuum. The residue is dissolved in 50 ml of ethyl acetate and washed successively with H₂O and then with saturated NaCl solution. After drying over MgSO₄ and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum to provide 0.190 g (yield = 29%) of the desired crystalline compound.

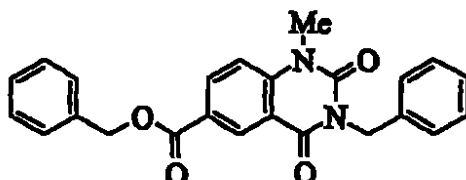
MS m/z 387.2 (M+H)⁺

NMR. DMSO ¹H δ (ppm) 5.06 (s, 2H), 5.34 (s, 2H); 7.22-7.46 (m, 10H), 8.20 (d, 1H), 8.48 (s, 1H), 11.89 (s, 1H)

CHN (C₂₃H₁₈N₂O₄) calc (%) C = 71.49, H = 4.70, N = 7.25

Found (%) C = 71.28, H = 4.94, N = 7.11

Example 38. Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate



0.084 g (0.217 mmol) of the product of Example 37 is stirred with anhydrous THF in apparatus protected from moisture and under an inert atmosphere. 0.14 ml of 1.6M BuLi in hexane (0.224 mmol) is introduced. The mixture is stirred for 10 minutes, followed by addition of 0.04 ml (0.642 mmol) of methyl iodide. The THF is removed under vacuum. The residue is dissolved in EtOAc and washed successively with H₂O and then with

saturated NaCl solution. After drying over MgSO_4 and concentration under vacuum, the crude product obtained is purified by flash chromatography on silica, eluting with a 50/50 mixture of hexane/EtOAc. The desired fractions are combined and the solvent is removed under vacuum. The pale yellow product is solidified in ether:

- 5 Weight: 0.049 g Yield = 56% MS m/z 401.2 (M+H)⁺
 NMR. DMSO ^1H δ (ppm) 3.31 (s, 3H), 5.12 (s, 2H), 5.37 (s, 2H), 7.21-7.60 (m, 11H), 8.28 (d, 1H), 8.58 (s, 1H)
 CHN ($\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4$) calc (%) C = 71.99, H = 5.03, N = 7.00
 Found (%) C = 71.71, H = 5.25, N = 6.87

10 **Example 39 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline
 -6-carboxylate**

The compound is obtained according to the procedure of Example 37, but using dichloromethane as solvent, the product is obtained as follows:

- MS m/z 388.2 (M+H)⁺
 15 NMR. DMSO ^1H δ (ppm) 5.07 (s, 2H), 5.41 (s, 2H), 7.20-7.32 (m, 6H), 7.43 (d, 2H), 8.26 (d, 1H), 8.53-8.58 (m, 3H), 11.93 (s, 1H)
 CHN ($\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}_4 \cdot 0.3\text{H}_2\text{O}$) calc (%) C = 67.27, H = 4.52, N = 10.70
 found (%) C = 67.32, H = 4.40, N = 10.47

20 **Example 40. 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4
 -tetrahydroquinazoline -6-carboxylate**

The compound is obtained according to the procedure of Example 37, but using the compound of Preparation C and 4-pyridylcarbinol.

- MS m/z 402.3 (M+H)⁺
 NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 5.14 (s, 2H), 5.42 (s, 2H), 7.23-7.33 (m, 5H), 7.43-
 25 7.45 (m, 2H), 7.60 (d, 1H), 8.32-8.36 (m, 1H), 8.57-8.64 (m, 3H)
 CHN ($\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_4 \cdot 0.14\text{H}_2\text{O}$) calc (%) C = 68.39, H = 4.81, N = 10.40
 found (%) C = 68.40, H = 4.71, N = 10.38

Example 41 Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

0 100 g (0.337 mmol) of compound of Preparation B and 1 ml of anhydrous THF are placed in a round-bottomed flask protected from moisture. The suspension is stirred and
5 0 24 g (0 150 ml, 2 025 mmol) of thionyl chloride is added. The mixture is refluxed for 1 h 30 min. After cooling, the solution is concentrated to dryness on a rotavapor. The 0 110 g of acid chloride obtained is used in the next stage without further purification.

0 080 g (0 51 mmol) of piperonyl alcohol, 1 ml of dichloromethane and 0 051 g (0 070 ml, 0 51 mmol) of triethylamine are introduced into a round-bottomed flask protected from
10 moisture. The solution is cooled to 0°C.

The above acid chloride suspended in 2 5 ml of dichloromethane is added to the solution.

The mixture is stirred at room temperature for 48 hours. The precipitate obtained is filtered off. The 0 050 g is purified by recrystallization from acetonitrile.

Weight: 0 025 g Yield = 17%

15 TLC CH₂Cl₂/MeOH 95/5 R_f = 0 85

NMR. DMSO ¹H δ (ppm) 5 1 (s, 2H), 5 25 (s, 2H), 6 05 (s, 2H), 6 9-7 4 (m, 9H), 8 2 (d, 1H), 8 5 (s, 1H), 11 9 (bs, 1H)

IR: 1715, 1650, 1624, 1446, 1285, 1262, 1080, 928, 865, 764 cm⁻¹

m.p. = 238 5°C

20 HPLC: 99 7%

Example 42: Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The compound is obtained (0 140 g) according to the procedure of Example 41, but using the compound of Preparation C and piperonyl alcohol

25 TLC CH₂Cl₂/MeOH 95/5 R_f = 0 85

NMR. DMSO ¹H δ (ppm) 3 55 (s, 3H), 5 15 (s, 2H), 5 30 (s, 2H), 6 05 (s, 2H), 6 9-7 4 (m, 8H), 7 6 (d, 1H), 8 25 (d, 1H), 8 6 (s, 1H)

IR: 1716, 1703, 1659, 1618, 1447, 1294, 1227, 1103, 935, 813, 763 cm⁻¹

m.p. = 199.5°C

HPLC 98.8%

Example 43: Benzyl 1-benzyl-2,4-dioxo-3-pyrid-4-ylmethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate

5 0.5 g (1.7 mmol) of compound obtained in the Step 3 of Example 20 in 15 ml of anhydrous THF is stirred and 0.2 ml (1.7 mmol) of benzyl chloride and 1.2 g (8.7 mmol) of K_2CO_3 are added. The mixture is stirred overnight at room temperature and treated as usual to provide the desired compound

MS m/z 478.2 (M+H)+

10 NMR. DMSO ^1H δ (ppm) 5.19 (s, 2H), 5.35 (s, 2H), 5.39 (s, 2H), 7.25-7.45 (m, 13H), 8.19 (d, 1H), 8.47-8.49 (m, 2H), 8.62 (s, 1H)

CHN ($C_{29}H_{23}N_3O_4$) calc (%) C = 72.94, H = 4.85, N = 8.80

Found (%) C = 72.58, H = 4.79, N = 8.57

Example 44 4-Pyridylmethyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate

15

0.69 g (2.3 mmol) of compound obtained in Step 3 of Example 21 is treated according to the procedure of Example 37, using 4-pyridylcarbinol. The product is obtained as follows

MS m/z 394.2 (M+H)+

20 NMR. DMSO ^1H δ (ppm) 5.21 (s, 2H), 5.40 (s, 2H), 6.93 (d, 1H), 7.11 (m, 1H), 7.28 (d, 1H), 7.40 (d, 1H), 7.40 (m, 2H), 8.24 (d, 1H), 8.49-8.59 (m, 3H)

CHN ($C_{20}H_{15}N_3O_4S \cdot 0.13 CH_2Cl_2 \cdot 0.03$ (ether))

Calc (%) C = 59.81, H = 3.86, N = 10.33,

Found (%) C = 59.79, H = 3.82, N = 10.32

Example 45: 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

25

The compound is obtained (0.040 g) according to the procedure of example 37, but using the compound obtained in the Step 3 of Example 28 and 4-pyridylcarbinol. The product is crystallized from methanol.

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.70$

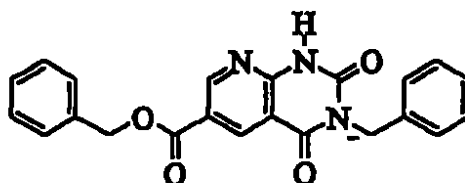
5 NMR. DMSO ^1H δ (ppm) 5.0 (s, 2H), 5.70 (s, 2H), 6.0 (s, 2H), 6.85 (s, 2H), 7.0 (s, 1H), 7.4 (d, 1H), 7.95-8.05 (m, 2H), 8.3-8.35 (m, 1H), 8.60 (s, 1H), 8.8-8.95 (m, 2H), 12.0 (m, 1H)

IR. 1710, 1670, 1622, 1501, 1440, 1279, 1236, 1041, 923, 764 cm^{-1}

m.p. = 204.4°C

HPLC 92.4%

10 **Example 46 Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate**



Step 1 3-Benzyl-6-methyl-1H-pyrido[2,3-d]pyrimidine-2,4-dione

20 g (111 mmol) of ethyl 2-amino-5-methylnicotinate and 200 ml of pyridine are brought to reflux. 13.7 ml (111 mmol) of benzyl isocyanate are added. Refluxing is continued overnight. After cooling, the precipitate is filtered off and washed with 2x100 ml of ethanol and 2x100 ml of ether.

Weight: 10 g in two crops Yield = 34%

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.5$

20 NMR. DMSO ^1H δ (ppm) 2.2 (s, 3H), 5.0 (s, 2H), 7.15-7.35 (m, 5H), 8.1 (s, 1H), 8.5 (s, 1H)

m.p. = 279°C

HPLC 97%

Step 2 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylic acid

25 3.0 g (11.2 mmol) of the product of the preceding Step 1, 100 ml of H_2O , 7.1 g (44.9 mmol) KMnO_4 and 10 ml of NMP are introduced into a round-bottomed flask. The reaction medium is refluxed overnight. The medium is filtered while hot. The filtrate

crystallizes after cooling. After filtering off the new precipitate, the filtrate is treated with 40 ml of Amberlite IR 120 (+) resin. The resin and acid mixture is filtered and the acid is extracted by washing with a 70/30 mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$. The solvent is removed under vacuum to provide 0.32 g of a white solid (yield = 10%)

5 NMR. DMSO ^1H δ (ppm) 5.0 (s, 2H), 7.15-7.25 (m, 5H), 8.65 (s, 1H), 9.1 (s, 1H), 12.4 (s, 1H)

Step 3 Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate

10 The esterification of the compound of the preceding Step 2 is carried out by the procedure described in Example 37, using benzyl alcohol.

After solidification in methanol, 0.040 g of the desired product is obtained (yield = 31%)

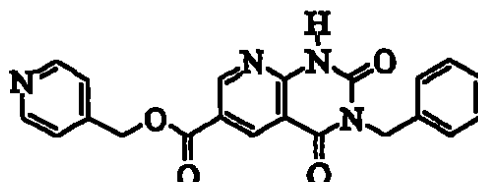
TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 R_f = 0.8

NMR. CDCl_3 ^1H δ (ppm) 5.2 (s, 2H), 5.4 (s, 2H), 7.2-7.6 (m, 10H), 9.05 (s, 1H), 9.3 (s, 1H), 10.9 (s, 1H)

15 m.p. = 223°C

HPLC. 93.1%

Example 47: 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate.



20 The compound is obtained with a yield of 20% (0.050 g) according to the procedure described in Example 37, but using the compound obtained in the Step 2 of example 46 and 4-pyridylcarbinol

TLC $\text{EtOAc}/\text{NH}_4\text{OH}$ 99/1 R_f = 0.6

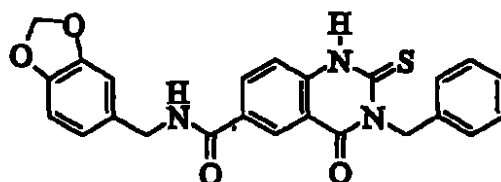
25 NMR. DMSO ^1H δ (ppm) 5.05 (s, 2H), 5.4 (s, 2H), 7.15-7.41 (m, 5H), 7.45 (d, 2H), 8.55 (d, 2H), 8.7 (s, 1H), 9.15 (s, 1H), 12.55 (s, 1H)

m.p. = 280°C

HPLC 97%

637

**Example 48: 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
(benzo[1,3]dioxol-5-ylmethyl)amide**



The synthesis is carried out according to Synthetic Scheme 1, using benzyl isothiocyanate during the cyclization to the 4-oxo-2-thioxoquinazoline. After saponification and amidation with piperonylamine, the expected compound is obtained.

Weight: 0.100 g TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 95/5 $R_f = 0.64$

NMR DMSO ^1H δ (ppm) 4.4 (d, 2H), 5.65 (s, 2H), 5.95 (s, 2H), 6.75-6.95 (m, 3H), 7.2-7.4 (m, 5H), 7.45 (d, 1H), 8.2 (d, 1H), 8.55 (s, 1H), 9.2 (t, 1H), 13.2 (bs, 1H)

IR: 1698, 1636, 1619, 1528, 1446, 1194, 1037, 768

m.p. = 249°C

HPLC 97.2%

Example 49 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

Into a stirred round-bottomed flask protected from moisture, 0.7 g (1.44 mmol) of compound of Example 34 and 70 ml of anhydrous dichloromethane are introduced. The mixture is stirred and 1.4 ml (14.4 mmol) of BBr_3 in 7 ml of dichloromethane are added dropwise. After 2 hours of stirring at room temperature the reaction is complete. After an usual treatment, 0.280 g of the desired product is obtained (yield = 42%).

TLC $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90/10 $R_f = 0.15$

NMR DMSO ^1H δ (ppm) 3.55 (s, 3H), 4.35 (d, 2H), 5.2 (s, 2H), 6.65 (d, 2H), 7.10 (d, 2H), 7.40 (d, 2H), 7.55 (d, 1H), 7.85 (d, 2H), 8.25 (d, 1H), 8.60 (s, 1H), 9.15 (t, 1H), 9.2 (s, 1H), 12.8 (bs, 1H)

IR 3403, 2553, 1697, 1658, 1615, 1507, 1482, 1423, 1247, 1109, 829, 752 cm^{-1}

M.P. = 174.0°C

HPLC 97.06%

**Example 50 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro
quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

0.3 g (0.64 mmol) of the compound of Example 35 is treated with a 2M solution of dimethylamine in THF according to the procedure described in Example 1. The crude product is purified by chromatography on silica gel and concentrated in ether to provide 0.160 g of the desired compound (yield 49.9%).

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

NMR. CDCl_3 ^1H δ (ppm) 2.90 (s, 3H), 3.05 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 4.60 (d, 2H), 5.25 (s, 2H), 6.60 (t, 1H), 6.85 (d, 2H), 7.3 (m, 5H), 7.45 (d, 2H), 8.25 (d, 1H), 8.50 (s, 1H)

IR 3378, 1710, 1654, 1641, 1618, 1508, 1476, 1246, 752 cm^{-1}

M.P. = 189 °C

HPLC 97 %

**Example 51 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro
-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of Example 50 but using methylamine.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.55$

NMR. DMSO ^1H δ (ppm) 2.75 (d, 3H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.85 (d, 2H), 7.25 (d, 2H), 7.35 (d, 2H), 7.55 (d, 1H), 7.75 (d, 2H), 8.25 (q, 1H), 8.35 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

IR 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P. = 255.1 °C

HPLC 97.0 %

**Example 52: 3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic
acid 4-methoxy-benzylamide**

640

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-allyl bromide.

5 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.8 (s,3H), 4.4 (d,2H), 4.55 (d,2H), 5.10-5.20 (m,2H), 5.80-5.95 (m,1H), 6.9 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.6 (s,1H), 9.25 (t,1H)

IR. 1703, 1642, 1615, 1508, 1477, 1246, 765 cm^{-1}

M.P. = 207 $^{\circ}\text{C}$

HPLC 98.9 %

10 **Example 53 1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1(2-bromoethyl)pyrrole.

15 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.7 (s,3H), 4.15 (m,2H), 4.25 (m,2H), 4.40 (d,2H), 5.90 (s,2H), 6.7 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.55 (s,1H), 9.2 (t,1H)

IR 3338, 1708, 1655, 1640, 1508, 1478, 1251, 117, 1032, 835, 734 cm^{-1}

M.P. = 147 $^{\circ}\text{C}$

20 HPLC 96.6 %

Example 54 1-Methyl-2,4-dioxo-3-(prop-2-ynyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and prop-2-ynyl bromide

25 NMR. DMSO ^1H δ (ppm) 3.15 (s,1H), 3.55 (s,3H), 3.7 (s,3H), 4.40 (d,2H), 4.70 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.25 (t,1H)

IR 3265, 1710, 1667, 1635, 1501, 1326, 1249, 1036, 825, 783, 752 cm^{-1}

M.P = 206 °C

HPLC 97.7 %

5 **Example 55 1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-3-methyl-but-2-ene

10 NMR. DMSO ^1H δ (ppm) 1.65 (s,3H), 1.75 (s,3H), 3.50 (s,3H), 3.7 (s,3H), 4.40 (d,2H), 4.55 (d,2H), 5.20 (t,1H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.25 (t,1H)

IR 3282, 1705, 1659, 1634, 1500, 1314, 1246, 826 cm^{-1}

M.P = 187 °C

15 HPLC 96.9 %

Example 56 1-Methyl-2,4-dioxo-3-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-(bromomethyl)pyridine

20 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.7 (s,3H), 4.40 (d,2H), 5.25 (s,2H), 6.90 (d,2H), 7.25 (m,3H), 7.35 (d,1H), 7.60 (d,1H), 7.70 (m,1H), 8.25 (d,1H), 8.40 (d,1H), 8.60 (s,1H), 9.2 (t,1H)

IR 1702, 1658, 1643, 1618, 1508, 1476, 1331, 1248, 751 cm^{-1}

25 M.P = 156 °C

HPLC 99.5 %

Example 57 3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-chloro-acetamide.

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.7 (s,3H), 4.40 (d,2H), 4.50 (s,2H), 6.90 (d,2H),
5 7.20 (s,1H), 7.25 (d,2H), 7.55 (d,1H), 7.65 (s,1H), 8.25 (d,1H), 8.60 (s,1H), 9.25 (t,1H)

IR 1655,1531,1508,1477,1303,1249,752 cm^{-1}

M.P = 269 °C

HPLC 99.2 %

10 **Example 58 1-Methyl-2,4-dioxo-3-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the-Step 1 of the Example 34 and 3-(bromomethyl)pyridine.

15 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.7 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.85 (d,2H), 7.20-7.40 (m,3H), 7.55 (d,1H), 7.75 (d,1H), 8.25 (m,1H), 8.45 (d,1H), 8.60 (m,2H), 9.20 (t,1H)

IR 1699, 1660, 1615, 1500, 1479, 1249, 1032, 752, 712 cm^{-1}

M.P = 140 °C

HPLC 89.6 %

20 **Example 59 :1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-bromomethyl-1-methyl-piperidine

NMR. DMSO ^1H δ (ppm) 0.85-1.00 (m, 1H), 1.30-1.45 (m, 1H), 1.55-2.05 (m, 5H), 2.10 (s, 3H), 2.60 (m, 2H), 3.55 (s, 3H), 3.75 (s, 3H); 3.85 (d, 2H), 4.40 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H); 7.50 (d, 1H), 8.25 (d, 1H), 8.60 (s, 1H), 9.25 (t, 1H)

IR 2926, 1655, 1641, 1508, 1247, 788 cm^{-1}

5 MP = 174 °C

HPLC 99.3 %

Example 60 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

10 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)benzonitrile

NMR DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.75 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.45-7.60 (m, 3H), 7.75 (d, 2H), 8.25 (d, 1H), 8.60 (s, 1H); 9.20 (t, 1H)

15 IR 3411, 2216, 1708, 1649, 1616, 1251, 839, 765 cm^{-1}

MP = 222 °C

HPLC 97.2 %

Example 61 3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

20 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-benzonitrile.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

25 NMR. DMSO ^1H δ (ppm) 3.45 (s, 3H), 3.70 (s, 3H), 4.45 (d, 2H), 5.15 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.55 (m, 2H), 7.70 (m, 2H), 7.80 (s, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.20 (t, 1H)

IR 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718 cm^{-1}

MP = 201 °C

HPLC 97.1 %

Example 62 3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

5 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 1-bromo-2-methoxy-ethane.

NMR. DMSO ^1H δ (ppm) 3.25 (s,3H), 3.55 (m,5H), 3.70 (s,3H); 4.15 (t,2H), 4.40 (d,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.20 (t,1H)

IR 3274, 1709, 1660, 1633, 1514, 1249, 1030, 823 cm^{-1}

10 M.P. = 200 °C

HPLC 99.2 %

Example 63 :3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

15 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-(bromomethyl)-1-methoxyphenyl

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,6H), 4.40 (d,2H), 5.10 (s,2H), 6.75-6.90 (m,5H), 7.15-7.30 (m,3H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.20 (t,1H)

IR 3387, 1704, 1657, 1640, 1616, 1509, 1250, 766 cm^{-1}

20 M.P. = 154 °C

HPLC 99.4 %

Example 64. 3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

25 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and bromomethylcyclopropyl

100

NMR. DMSO- ^1H δ (ppm) 0.40 (m, 4H), 1.2 (m, 1H), 3.55 (s, 3H), 3.70 (s, 3H), 3.85 (d, 2H), 4.40 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.55 (d, 1H), 8.25 (m, 1H), 8.60 (d, 1H); 9.20 (t, 1H)

IR 3282, 1703, 1657, 1634, 1502, 1258, 1028, 829, 752 cm^{-1}

M.P. = 209 $^{\circ}\text{C}$

5 HPLC 98.2 %

Example 65 1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(2-bromoethyl)morpholine

10

NMR. DMSO ^1H δ (ppm) 2.40 (m, 4H), 2.55 (m, 2H), 3.50 (m, 7H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.55 (d, 1H), 8.25 (d, 1H), 8.60 (s, 1H), 9.20 (t, 1H)

IR 3419, 1707, 1656, 1612, 1506, 1475, 1246, 1111, 752 cm^{-1}

15

M.P. = 135 $^{\circ}\text{C}$

HPLC 98.5 %

Example 66: 3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and (bromomethyl)cyclohexane.

20

NMR. DMSO ^1H δ (ppm) 0.9-1.20 (m, 5H), 1.5-1.85 (m, 6H), 3.55 (s, 3H), 3.70 (s, 3H), 3.80 (d, 2H), 4.40 (d, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.50 (d, 1H), 8.25 (m, 1H), 8.60 (s, 1H), 9.20 (t, 1H)

25

IR 3378, 2918, 1703, 1654, 1640, 1508, 1478, 1329, 1244, 789, 767 cm^{-1}

M.P. = 183 $^{\circ}\text{C}$

HPLC 99.0 %

641

Example 67: 1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-phenylpropyl bromide

NMR. DMSO ^1H δ (ppm) 1.90 (m,2H), 2.65 (t,2H), 3.50 (s,3H), 3.70 (s,3H), 4.0 (t,2H), 4.40 (d,2H), 6.85 (d,2H), 7.10-7.30 (m,7H), 7.50 (d,1H), 8.20 (m,1H), 8.60 (s,1H), 9.20 (t,1H)

IR 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749 cm^{-1}

M.P = 167 $^{\circ}\text{C}$

HPLC 98.8 %

Example 68: 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-(bromomethyl)-fluorobenzene.

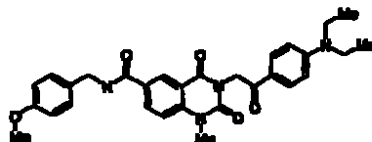
NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.1 (s,2H), 6.90 (d,2H), 7.10 (t,2H), 7.25 (d,2H), 7.40 (m,2H), 7.50 (d,1H), 8.25 (m,1H), 8.60 (s,1H), 9.20 (t,1H)

IR 3395, 1704, 1641, 1615, 1509, 1477, 1327, 1245, 1032, 749 cm^{-1}

M.P = 180 $^{\circ}\text{C}$

HPLC 99.4 %

Example 69. 3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-Chloro-1-(4-diethylamino-phenyl)-ethan-1-one.

NMR. DMSO ¹H δ (ppm) 1.15 (t, 6H), 3.30-3.50 (m, 4H), 3.60 (s, 3H), 3.75 (s, 3H), 4.45 (d, 2H), 5.35 (s, 2H), 6.75 (d, 2H), 6.90 (d, 2H), 7.30 (d, 2H), 7.65 (d, 1H), 7.90 (d, 2H), 8.30 (m, 1H), 8.60 (s, 1H), 9.25 (t, 1H)

IR 3370, 1670, 1655, 1596, 1504, 1258, 1242, 1190, 808 cm⁻¹

MLP = 237 °C

HPLC 97.0 %

Example 70: Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-acetate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 2-chloro-acetate

NMR. DMSO ¹H δ (ppm) 1.20 (t, 3H), 3.60 (s, 3H), 3.70 (s, 3H), 4.15 (q, 2H), 4.40 (d, 2H), 4.70 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.60 (d, 1H), 8.30 (m, 1H), 8.60 (s, 1H), 9.20 (t, 1H)

IR 1711, 1668, 1637, 1508, 1247, 1212, 1032, 835, 752 cm⁻¹

MLP = 170 °C

HPLC 97.7 %

Example 71 3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 2-bromoethan-1-ol

NMR. DMSO ¹H δ (ppm) 3.50-3.65 (s, 5H), 3.70 (s, 3H), 4.05 (t, 2H), 4.40 (d, 2H), 4.80 (t, 1H), 6.90 (d, 2H), 7.25 (d, 2H), 7.50 (s, 1H); 8.25 (m, 1H), 8.60 (s, 1H), 9.25 (t, 1H)

IR : 3290, 1702, 1654, 1639, 1619, 1509, 1327, 1240, 1071, 835, 753 cm⁻¹

642

M.P = 168 °C

HPLC 96.7 %

Example 72 Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionate

5 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-bromo-propionate.

NMR. DMSO ¹H δ (ppm) 2.60 (t,2H), 3.50 (s,3H), 3.60 (s,3H), 3.70 (s,3H), 4.20 (t,2H), 4.40 (d,2H), 6.90 (d,2H), 7.25 (d,2H), 7.50 (d,1H), 8.25 (dd,1H), 8.60 (s,1H), 9.25 (t,1H)

10 IR 3411, 2361, 1704, 1656, 1644, 1618, 1508, 1478, 1328, 1244, 853, 766 cm⁻¹

M.P = 154.8 °C

HPLC 95.1 %

Example 73 .3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionic acid

15

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 72.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.25

NMR. DMSO ¹H δ (ppm) 2.50 (t,2H), 3.55 (s,3H); 3.70 (s,3H); 4.15 (t,2H), 4.40 (d,2H), 6.85 (d,2H), 7.25 (d,2H), 7.50 (d,1H), 8.25 (dd,1H), 8.55 (s,1H), 9.15 (t,1H), 12.3 (bs,1H)

20

IR . 3395, 2353, 1701, 1656, 1639, 1508, 1478, 1244, 1040, 839, 799, 754 cm⁻¹

M.P = 201.5 °C

HPLC 96.4 %

Example 74 : Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyrate

25

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and ethyl 4-bromobutyrate.

NMR. DMSO ^1H δ (ppm) 1.10 (t,3H), 1.90 (q,2H), 2.30 (t,2H), 3.55 (s,3H), 3.70 (s,3H),
5 4.00 (bs,4H), 4.45 (d,2H), 6.90 (d,2H), 7.25 (d,2H), 7.50 (d,1H); 8.20 (dd,1H), 8.60 (s,1H), 9.15 (t,1H)

IR $\cdot$ 3378, 2943, 1704, 1657, 1647, 1617, 1509, 1477, 1246, 1178, 1030, 751 cm^{-1}

M.P = 138.9 $^{\circ}\text{C}$

HPLC $\cdot$ 99.1 %

10 **Example 75 : 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyric acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 74

15 TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.50

NMR. DMSO ^1H δ (ppm) 1.80 (q,2H), 2.25 (t,2H), 3.50 (s,3H), 3.70 (s,3H), 4.0 (t,2H),
4.40 (d,2H), 6.90 (d,2H), 7.25 (d,2H), 7.50 (d,1H), 8.25 (dd,1H), 8.60 (s,1H), 9.20 (t,1H),
12.0 (bs,1H)

IR $\cdot$ 3346, 1691, 1651, 1637, 1512, 1234, 1248, 1178, 1024, 835, 752 cm^{-1}

20 M.P = 165.6 $^{\circ}\text{C}$

HPLC $\cdot$ 99.1 %

Example 76: Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetate

25 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-(bromomethyl)phenyl acetate

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.60 (s,3H), 3.65 (s,2H), 3.70 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 6.90 (d,2H), 7.10-7.35 (m,6H), 7.55 (d,1H), 8.25 (dd,1H), 8.65 (s,1H), 9.20 (t,1H)

IR 3370, 2951, 1707, 1655, 1639, 1616, 1509, 1328, 1251, 1157, 1036, 766 cm^{-1}

5 M.P = 173.2 $^{\circ}\text{C}$

HPLC 99.0 %

Example 77 {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid

10 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B, but using as substrates the compound obtained in the Example 76

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.50

NMR. DMSO ^1H δ (ppm) 3.55 (s,2H), 3.60 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 6.90 (d,2H), 7.10-7.35 (m,6H), 7.55 (d,1H), 8.25 (dd,1H), 8.60 (s,1H), 9.20 (t,1H), 12.3 (bs,1H)

15 IR 3378, 1706, 1653, 1640, 1616, 1508, 1330, 1249, 1149, 1032, 823, 766 cm^{-1}

M.P = 165 $^{\circ}\text{C}$

HPLC 96.7 %

Example 78 :3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

20 The compound is obtained from the compound obtained in Example 77, which is transformed in situ into the acid chloride derivate by action of oxalyle chloride and then treated with a 2M solution of dimethylamine in THF

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.50

25 NMR. DMSO ^1H δ (ppm) 2.80 (s,3H), 3.0 (s,3H), 3.55 (s,3H), 3.60 (s,2H), 3.75 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 6.90 (d,2H), 7.15 (d,2H), 7.25 (d,4H), 7.55 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

IR 3308, 2926, 1706, 1665, 1640, 1504, 1474, 1320, 1250, 1133, 1036, 834 cm^{-1}

MP = 183 °C

HPLC 93.2 %

Example 79 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

- 5 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 3-((E)-3-chloro-propenyl)-pyridine.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.63

- 10 NMR. DMSO ¹H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 4.75 (d,2H), 6.40-6.50 (m,1H), 6.50-6.60 (d,1H), 6.90 (d,2H), 7.20-7.35 (m,3H), 7.55 (d,1H), 7.85 (d,1H), 8.25 (d,1H), 8.40 (s,1H), 8.60 (d,2H), 9.20 (t,1H)

IR 3395, 1703, 1643, 1509, 1479, 1254, 761 cm⁻¹

MP = 200.0 °C

HPLC 98.7 %

- 15 **Example 80 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-((E)-3-chloro-propenyl)-pyridine.

- 20 TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.43

NMR. DMSO ¹H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 4.45 (d,2H), 4.80 (d,2H), 6.55 (d,1H), 6.60-6.70 (m,1H), 6.90 (d,2H), 7.25 (d,2H), 7.35 (d,2H), 7.55 (d,1H), 8.25 (dd,1H), 8.45 (d,2H), 8.65 (s,1H), 9.20 (t,1H)

IR 3395, 1704, 1643, 1509, 1479, 1332, 1254, 980, 765 cm⁻¹

- 25 MP = 241 °C

HPLC 98.1 %

644

Example 81 : 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-bromomethyl-benzenesulfonamide

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.48$

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.30 (s, 2H); 7.50 (d, 2H), 7.55 (d, 1H), 7.75 (d, 2H), 8.25 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

IR 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P = 219.0 °C

HPLC . 94.9 %

Example 82 : 3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the Step 1-5 to 2-5 of the preparation B using 3-(4-methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid.

NMR. DMSO ^1H δ (ppm) 3.20 (s, 3H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H); 5.25 (s, 2H), 6.90 (d, 2H), 7.15 (d, 2H), 7.50-7.60 (m, 3H), 7.85 (d, 2H), 8.30 (dd, 1H), 8.60 (s, 1H), 9.20 (t, 1H)

IR 3370, 1707, 1658, 1641, 1303, 1148, 783 cm^{-1}

M.P = 210 °C

HPLC 97.9 %

Example 83 : 3-(4-Dimethylsulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide

Step 1 Methyl 3-(4-chlorosulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

Into a stirred round-bottomed flask protected from moisture, 3.2 ml (47.5 mmol) of chlorosulfonic acid are introduced. The mixture is cooled with an ice bath and 2.2 g (6.80 mmol) of compound obtained in the Step 1 of Preparation C are added slowly. After 3 hours stirring at room temperature, the reaction mixture is poured in an mixture of water and ice. The precipitate is filtered and dried to provide 1.8 g of the desired product.

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.90 (s, 3H), 5.15 (s, 2H), 7.25 (m, 2H), 7.50-7.60 (m, 3H), 8.25 (dd, 1H), 6.0 (s, 1H)

Step 2 Methyl 3-(4-dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

To a stirred solution of 0.4 g (0.94 mmol) of the compound obtained in the preceding Step 1 in 25 ml of dichloromethane are added 3.3 ml (66 mmol) of dimethylamine 2M in THF. After 1 hour, the reaction mixture is concentrated under vacuum. A chromatography on silica gel (dichloromethane/acetone: 98/2) provides 0.370 g (yield 91%) of the desired product.

NMR. DMSO ^1H δ (ppm) 2.6 (s, 6H), 3.6 (s, 3H), 3.9 (s, 3H), 5.25 (d, 2H), 7.60 (m, 3H), 7.70 (m, 2H), 8.25 (dd, 1H), 8.60 (s, 1H)

Step 3 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B, using as substrate the compound obtained in the preceding Step 2.

NMR. DMSO ^1H δ (ppm) 2.60 (s, 6H), 3.55 (s, 3H), 5.25 (s, 2H), 7.60 (m, 3H), 7.70 (m, 2H), 8.25 (dd, 1H), 8.60 (s, 1H), 13.20 (bs, 1H)

Step 4 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 1, but using 4-methoxybenzylamine. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.48

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NMR. DMSO ^1H δ (ppm) 2.55 (s,6H), 3.55 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.25 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55-7.60 (m,3H), 7.60-7.70 (m,2H), 8.30 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

IR 1708, 1660, 1618, 1503, 1477, 1335, 1247, 1160, 952, 760, 718 cm^{-1}

5 M.P. = 112 $^{\circ}\text{C}$

HPLC 94.8 %

Example 84 . 3-[4-(2-Dimethylamino-ethylsulfamoyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

10 The compound is obtained according the procedure of Steps 1 to 4 of the Example 83 using *N,N*-dimethylethylene diamine in the Step 2. The desired compound crystallizes in a mixture of dichloromethane/ether.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.47

15 NMR. DMSO ^1H δ (ppm) 2.0-2.15 (m,6H), 2.20-2.35 (m,2H), 2.75-2.85 (m,2H), 3.55 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.85 (d,2H), 7.25 (d,2H), 7.45-7.65 (m,4H), 7.65-7.80 (m,2H), 8.25 (d,1H), 8.60 (m,1H); 9.20 (m,1H)

IR 1707, 1656, 1618, 1508, 1477, 1326, 1249, 1155 cm^{-1}

M.P. = 114 $^{\circ}\text{C}$

HPLC 90.9 %

20 **Example 85 : 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

Step 1 Methyl 1-methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

25 The compound is obtained according the procedure of Steps 1 to 3 of the Example 83 using methylamine in the Step 2.

Step 2 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.2 g (0.5 mmol) of the compound obtained in the preceding Step 1 is dissolved in 10 ml of dichloroethane. The solution is cooled and 3.2 ml (6.4 mmol) of trimethylaluminum 2M in toluene and 0.875 g (6.4 mmol) of 4-methoxy-benzylamine are added. The solution mixture is stirred overnight at room temperature and then 24 hours at 60°C. The solution is evaporated under vacuum and a chromatography over silica gel (dichloromethane/ether) provides 0.085 g (yield 32%) of the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.60

NMR. DMSO ^1H δ (ppm) 2.40 (d, 3H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.85 (d, 2H), 7.25 (d, 2H), 7.40 (q, 1H), 7.50 (d, 2H), 7.60 (d, 1H), 7.70 (d, 2H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H)

IR 3338, 1708, 1654, 1616, 1548, 1507, 1329, 1245, 1036, 825, 751 cm^{-1}

M.P. = 217.0 °C

HPLC 95.0 %

Example 86 Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 3-(bromomethyl)benzoate.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

NMR. DMSO ^1H δ (ppm) 3.50 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.40 (d, 2H), 5.2 (s, 2H), 6.80-6.90 (m, 2H), 7.2-7.3 (m, 2H), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 1H), 7.6-7.7 (m, 1H), 7.8-7.9 (m, 1H), 7.95 (s, 1H), 8.30 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

IR 3254, 1729, 1705, 1659, 1637, 1502, 1299, 1249, 749 cm^{-1}

M.P. = 193.5 °C

HPLC 100 %

Example 87 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

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The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 86

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

5 NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.40-7.45 (m,1H), 7.5-7.65 (m,2H), 7.80 (d,1H), 7.95 (s,1H), 8.20 (d,1H), 8.60 (s,1H), 9.2 (t,1H), 12.95 (s,1H)

IR 3400, 3190, 1705, 1659, 1646, 1616, 1510, 1247, 1197, 750 cm^{-1}

M.P. = 182 °C

HPLC 98.8 %

10 **Example 88 (E) Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoate**

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 4-bromocrotonate.

15 TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.75$

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.60 (s,3H), 3.70 (s,3H), 4.45 (d,2H), 4.75 (d,2H), 5.9 (d,1H), 6.80-6.90 (m,2H), 6.9-6.95 (m,1H), 7.2-7.3 (m,2H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.2 (t,1H)

IR 3408, 1708, 1644, 1617, 1507, 1477, 1280, 1248, 1036, 765 cm^{-1}

20 M.P. = 107.9 °C

HPLC 96.2 %

Example 89 . 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-but-2-enoic acid

25 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using as substrate the compound of the Example 88

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.50$

NMR. DMSO ^1H δ (ppm) 3.50 (s,3H); 3.70 (s,3H), 4.30 (d,2H), 4.70 (d,2H), 5.70-5.80 (m,1H), 6.70-6.85 (m,1H), 6.90 (d,2H), 7.25 (d,2H), 7.50 (d,1H), 8.20-8.25 (m,1H); 8.60 (s,1H), 9.2 (t,1H), 12.3 (bs,1H)

IR 3409, 1700, 1644, 1617, 1506, 1304, 1248, 767 cm^{-1}

5 M.P = 245.5 °C

HPLC 91.3 %

Example 90 : Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylate

10 The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-(chloromethyl)-2-furoate

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.60

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.55 (d,1H), 6.85 (d,2H), 7.25 (m,3H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.2 (t,1H).

15 IR 3249, 1711, 1664, 1636, 1503, 1446, 1299, 1250, 1148, 1023, 824, 765 cm^{-1}

M.P = 195.5 °C

HPLC 99.2 %

Example 91 . 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-furan-2-carboxylic acid

20 The compound is obtained by hydrolysis, in the presence of K_2CO_3 in a mixture of dioxane/water, of the compound of the Example 90

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.10

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.40 (s,2H), 5.20 (s,2H), 6.50 (s,1H), 6.90 (d,2H), 7.10 (s,1H), 7.25 (d,2H), 7.55 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.2 (t,1H), 13.05 (bs,1H)

25

IR 1711, 1661, 1618, 1505, 1477, 1326, 1248, 1141, 1024, 968, 824, 787 cm^{-1}

M.P = 198 °C

HPLC 100.0 %

Example 92 Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylate

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and methyl 5-bromomethyl-thiophene-2-carboxylate. This compound is obtained according to the procedure described in *J. Med. Chem.*, 1998, 41 (1), 74-95.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.20$

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.40 (d, 2H), 5.30 (s, 2H), 6.90 (d, 2H), 7.15 (d, 1H), 7.25 (d, 2H), 7.55 (d, 1H), 7.60 (d, 1H), 8.25 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

IR 3249, 1707, 1660, 1635, 1515, 1326, 1294, 1092, 1036, 625, 749 cm^{-1}

M.P. = 200.5°C

HPLC 91.5 %

Example 93 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-thiophene-2-carboxylic acid

The compound is obtained by hydrolysis, in the presence of K_2CO_3 in a mixture of dioxane/water, of the compound of the Example 92.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.25$

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.30 (s, 2H), 6.90 (d, 2H), 7.15 (d, 1H), 7.25 (d, 2H), 7.55 (m, 2H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H), 13.0 (m, 1H)

IR 3241, 1705, 1662, 1632, 1541, 1325, 1246, 1032, 921, 826, 783 cm^{-1}

M.P. = 198.5°C

HPLC 92.2 %

Example 94 : 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of the Example 34 but using as substrates the compound obtained in the Step 1 of the Example 34 and 4-nitrobenzyl bromide.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.47$

5 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.25 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.50-7.65 (m,3H), 8.15 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.2 (t,1H)

IR 1706,1661, 1618, 1513, 1477, 1345, 1248, 752 cm^{-1}

MP = 129.0 °C

HPLC 100 %

10 **Example 95 . 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

1 g (2.1 mmol) of the compound of Example 94 is hydrogenated with Pd/C in a mixture of dichloromethane/methanol 80/20 v/v. After 2 hours of stirring under hydrogen atmosphere, the reaction mixture is filtered. The solvent is removed under vacuum and the crude product is concretized from a mixture of dichloromethane/ether to provide 0.800 g of the desired compound (yield: 85.8%).

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.19$

15 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H); 3.70 (s,3H), 4.45 (d,2H), 4.90-5.05 (m,4H), 6.45 (d,2H), 6.90 (d,2H), 7.05 (d,2H), 7.25 (d,2H), 7.50 (d,1H), 8.25 (d,1H), 8.60 (s,1H), 9.2 (t,1H)

IR 3387, 1701, 1647, 1615, 1511, 1478, 1245, 789 cm^{-1}

MP = 167 °C

HPLC 99.0 %

25 **Example 96 3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

To a round bottom flask protected from the moisture are added successively 0.220 g (0.5 mmol) of the compound of Example 95 in 5 ml of CH_3CN , and under stirring 0.150 g (5

mmol) of powder of paraformaldehyd, 0.095 g (1.5 mmol) of NaBH_3CN and 100 μl of acetic acid. After 2 hours at room temperature and 1h30 under reflux, the reaction mixture is taken up in dichloromethane and washed with a solution of NaOH 1M. The organic phase is decanted, washed, dried and then concentrated under vacuum. The product is recrystallized from acetonitrile to provide 0.130 g (yield 55%) of the desired compound.

5 TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.42$

NMR. DMSO ^1H δ (ppm) 2.80 (s, 6H), 3.50 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.00 (s, 2H), 6.60 (d, 2H), 6.90 (d, 2H), 7.15-7.25 (m, 4H), 7.50 (d, 1H), 8.20 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

10 IR : 1699, 1654, 1640, 1616, 1508, 1324, 1324 cm^{-1}

MP = 205 $^{\circ}\text{C}$

HPLC 98.9 %

Example 97 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

15 To a round bottom protected from the moisture is added 0.190 g (0.43 mmol) of the compound of Example 95 in 10 ml of dichloromethane. The solution is stirred and 36 μl (40 mg, 0.51 mmol) of acetyl chloride and 72 μl of triethylamine are added. After 1 hour at room temperature 36 μl of acetyl chloride and 72 μl of triethylamine are added. After 1 hour, the organic phase is washed with a solution of HCl 1M and dried. A chromatography

20 over silica gel (dichloromethane/ether) provides 0.120 g (yield 57%) of the desired product.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.17$

NMR. DMSO ^1H δ (ppm) 2.0 (s, 3H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.05 (s, 2H), 6.90 (d, 2H), 7.20-7.30 (m, 4H), 7.45 (d, 2H), 7.50 (d, 1H), 8.25 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H), 9.85 (s, 1H)

25 IR 3330, 1661, 1617, 1511, 1475, 1322, 1244, 825, 752 cm^{-1}

MP = 251 $^{\circ}\text{C}$

HPLC : 100.0 %

Example 98 : 3-[4-(N,N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and methanesulfonyl chloride

5 TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR. DMSO ^1H δ (ppm) 3.50 (s, 6H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.40-7.50 (m, 4H), 7.55 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H)

IR . 1655, 1639, 1507, 1376, 1252, 1157, 905, 761 cm^{-1}

10 M P = 198 °C

HPLC 100.0 %

Example 99 . 3-(Benzofurazan-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-bromomethyl benzofurazan.

15 TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.80

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.25 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.60 (m, 2H), 7.90 (s, 1H), 8.0 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.2 (t, 1H)

IR 2370, 1701, 1653, 1617, 1499, 1477, 1326, 1243, 1181, 1028, 881, 781 cm^{-1}

20 M.P = 140.5 °C

HPLC : 100.0 %

Example 100 . 3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 4-fluorophenoxyethyl bromide

25

TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.60

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.20 (d,2H), 4.3-4.4 (m,2H), 4.4-4.50 (m,2H), 6.80-7.0 (m,4H), 7.0-7.1 (m,2H), 7.2-7.30 (m,2H), 7.4-7.5 (m,1H), 8.20-8.30 (m,1H), 8.60-8.70 (m,1H), 9.2 (t,1H)

IR 1707, 1656, 1641, 1520, 1475, 1247, 1209, 1034, 828, 752 cm^{-1}

5 M.P = 159.6 °C

HPLC 99.7 %

Example 101 :3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 2-chloroethyl phenyl sulphone.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.55

15 NMR. DMSO ^1H δ (ppm) 3.50 (s,3H), 3.6-3.70 (m,2H), 3.75 (s,3H), 4.3 (d,2H), 4.4-4.50 (m,2H), 6.90 (d,2H), 7.30 (d,2H), 7.4-7.7 (m,4H), 7.9 (d,2H), 8.20 (d,1H), 8.60 (s,1H), 9.2 (t,1H)

IR 3274, 1708, 1663, 1638, 1514, 1499, 1249, 1147, 1034, 825, 746 cm^{-1}

M.P = 192.9 °C

HPLC 96.0 %

20 **Example 102 :3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 4-chloromethyl-2-fluoro-1-methoxy-benzene.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

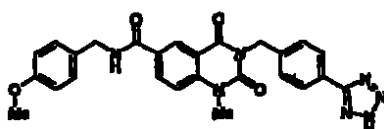
25 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 3.80 (s,3H), 4.4 (d,2H), 5.10 (s,2H), 6.90 (d,2H), 7.20 (m,5H), 7.55 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.2 (t,1H)

IR 3411, 2362, 1705, 1644, 1617, 1513, 1325, 1275, 1246, 1028, 827, 786 cm^{-1}

M.P = 136 °C

HPLC 100 0 %

Example 103: 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide



5

A solution of 3 g (6.6 mmol) of compound of the Example 60 in 100 ml of toluene, 1.3 g (19.8 mmol) of NaN_3 and 2.72 g (19.8 mmol) of triethylamine hydrochloride are heated at 80°C under an inert atmosphere. After 5 hours, 10 ml of DMF are added and the reflux is maintained overnight. After cooling, the precipitate is filtered and washed successively with AcOEt, MeOH and HCl 3N. The solid obtained is treated under reflux by a mixture of AcOEt/MeOH and filtered. A chromatography over silica gel (DMF with NH_4OH 10%) provides 1.2 g of the desired compound (yield 36%).

10

TLC CH_2Cl_2 / MeOH 80/20 R_f = 0.30

NMR. DMSO ^1H δ (ppm) 3.50 (bs, 1H), 3.55 (s, 3H), 3.70 (s, 3H), 4.4 (m, 2H), 5.20 (s, 2H), 6.90 (m, 2H), 7.25 (m, 2H), 7.50 (m, 3H), 8.0 (m, 2H), 8.3 (m, 1H), 8.70 (s, 1H), 9.2 (m, 1H).

15

M.P = 286°C

HPLC 96.7 %

Example 104: 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

20

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 3-(4-chloromethyl-phenyl)-5-methyl-[1,2,4]oxadiazole (which is obtained in 4 steps from 4-hydroxymethyl-benzonitrile).

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.50

25

NMR. CDCl_3 ^1H δ (ppm) 2.60 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 4.55 (m, 2H), 5.25 (s, 2H), 6.60 (s, 1H), 6.85 (m, 2H), 7.30 (m, 3H), 7.55 (m, 2H), 7.90 (m, 2H), 8.3 (m, 1H), 8.50 (s, 1H).

M.P = 235.0°C

650

HPLC 95.1 %

Example 105 : 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

To a round bottom containing 4Å molecular sieves, 5 ml of DMF, 76 mg (1.02 mmol) of *N*-hydroxy-acetamidine and 25 mg (1.02 mmol) of NaH are introduced. The mixture is stirred for 15 minutes and 0.5 g (1.02 mmol) of compound of the Example 34 is added. The reaction is heated at 65°C for 4 hours and then filtered over Celite. The filtrate is poured onto 100 ml of water. The precipitate obtained is filtered, washed successively by ethanol, water and ether, and dried to provide 0.210 g (yield: 40%) of the desired compound.

10 TLC CH₂Cl₂ / MeOH 95/5 R_f = 0.50

NMR. DMSO ¹H δ (ppm) 3.3 (s, 3H), 3.55 (s, 3H), 3.70 (s, 3H), 4.40 (m, 2H), 5.25 (s, 2H), 6.90 (m, 2H), 7.25 (m, 2H), 7.55 (m, 3H), 8.0 (d, 2H), 8.3 (m, 1H), 8.60 (s, 1H), 9.2 (m, 1H)

M.P. = 226 °C

HPLC 98.6 %

15 **Example 106 : Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 2-chloro-4-chloromethyl-benzoate

20

NMR. DMSO ¹H δ (ppm) 3.55 (s, 3H), 3.70 (s, 3H), 3.80 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.90 (m, 2H), 7.25 (m, 3H), 7.60 (d, 1H), 7.75 (d, 1H), 7.95 (s, 1H), 8.3 (m, 1H); 8.70 (s, 1H), 9.2 (m, 1H)

M.P. = 229 °C

25 HPLC 98.8 %

Example 107 : 2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

120

The compound is obtained by hydrolysis of the compound of Example 106 with a solution of aqueous methanol and K_2CO_3

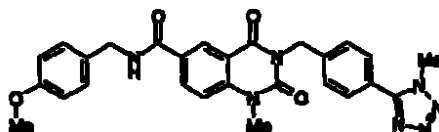
TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.30

5 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.40 (m,2H), 5.20 (s,2H), 6.85 (m,2H), 7.20 (m,3H), 7.60 (m,1H); 7.70 (m,1H), 7.95 (m,1H), 8.3 (m,1H), 8.60 (s,1H), 9.2 (m,1H), 13.2 (s,1H)

MP = 216 $^{\circ}C$

HPLC 96.5 %

10 **Example 108 : 1-Methyl-3-[4-(1-methyl-1H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-1-methyl-1H-tetrazole

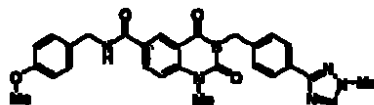
15 TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.40

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 4.10 (s,3H), 4.40 (m,2H), 5.20 (s,2H), 6.80 (d,2H), 7.25 (d,2H), 7.50 (m,3H), 7.80 (m,2H), 8.2 (d,1H), 8.60 (s,1H); 9.2 (s,1H)

MP = 143 $^{\circ}C$

HPLC = 100 %

20 **Example 109 : 1-Methyl-3-[4-(2-methyl-2H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**



25 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and 5-(4-chloromethyl-phenyl)-2-methyl-2H-tetrazole.

TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.50

851

121

NMR DMSO ^1H δ (ppm) 3.50 (s,3H), 3.70 (s,3H), 4.40 (m,5H), 5.20 (s,2H), 6.90 (m,2H), 7.25 (m,2H), 7.50 (m,3H), 8.0 (m,2H), 8.3 (d,1H), 8.60 (s,1H), 9.2 (m,1H)

M.P = 226 $^{\circ}\text{C}$

HPLC 98.2 %

5 **Example 110 :Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methoxy-benzoate.

10 **TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.60**

NMR. CDCl_3 ^1H δ (ppm) 3.60 (s,3H), 3.80 (s,3H), 3.85 (s,3H), 3.90 (s,3H), 4.55 (d,2H), 5.20 (s,2H), 6.45 (m,1H), 6.80 (d,2H), 7.05 (d,1H), 7.20 (m,4H), 7.70 (d,1H), 8.3 (d,1H), 8.50 (s,1H).

M.P = 170 $^{\circ}\text{C}$

15 **HPLC 98.6 %**

Example 111 :2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid

20 The compound is obtained by hydrolysis of compound of the Example 110 using as reagent K_2CO_3 in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.50

25 **NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 3.80 (s,3H), 4.40 (s,2H), 5.15 (s,2H), 6.90 (m,3H); 7.10 (s,1H), 7.30 (m,2H), 7.60 (m,2H), 8.3 (m,1H), 8.60 (s,1H), 9.2 (m,1H), 12.5 (bs,1H)**

M.P = 189 $^{\circ}\text{C}$

HPLC. 100.0 %

Example 112 :Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

To a stirred solution of 1 g (1.93 mmol) of compound of the Example 111 in 15 ml of dichloromethane, maintained at 0°C, are added dropwise, under an inert atmosphere, 7.7 ml (7.7 mmol) of BCl₃ 1M/l in dichloromethane. After 15 minutes of stirring at 0°C and 1 hour at room temperature, the reaction mixture is poured on ice and extracted by ethyl acetate. The organic phase is dried and concentrated under vacuum. The precipitate obtained is purified by chromatography over silica gel (dichloromethane/methanol 99/1) to provide 0.460 g (yield 47%) of the desired product.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.60

NMR. DMSO ¹H δ (ppm) 3.50 (s,3H), 3.70 (s,3H), 3.85 (s,3H), 4.40 (d,2H), 5.10 (s,2H), 6.85 (m,4H), 7.25 (d,2H), 7.55 (d,1H), 7.70 (d,1H), 8.3 (m,1H), 8.60 (s,1H), 9.2 (m,1H), 10.5 (s,1H)

M.P = 205.0 °C

HPLC . 100.0 %

Example 113 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K₂CO₃ in a mixture of methanol and water. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.60

NMR. DMSO ¹H δ (ppm) 3.50 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 6.80 (m,4H), 7.25 (m,2H), 7.55 (m,1H), 7.70 (d,1H), 8.3 (m,1H); 8.60 (s,1H); 9.2 (m,1H), 11.3 (bs,1H), 13.8 (s,1H)

M.P = 262.0 °C

HPLC 98.2 %

Example 114 :Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and methyl 4-bromomethyl-2-methyl benzoate.

TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.80

5 NMR. DMSO ^1H δ (ppm) 2.5 (s,3H), 3.50 (s,3H), 3.70 (s,3H), 3.80 (s,3H), 4.40 (s,2H), 5.10 (s,2H), 6.90 (m,2H), 7.25 (m,4H), 7.50 (d,1H), 7.70 (d,1H), 8.2 (m,1H), 8.60 (s,1H), 9.2 (s,1H)

M.P. = 167 °C

HPLC 100.0 %

10 **Example 115 : 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained by hydrolysis of compound of the Example 114 using first as reagent K_2CO_3 in a mixture of methanol and water, and secondly LiOH in reflux for 2 days. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired compound.

15 TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.50

NMR. DMSO ^1H δ (ppm) 2.5 (s,3H), 3.55 (s,3H), 3.80 (s,3H), 4.40 (d,2H), 5.10 (s,2H), 6.80 (d,2H), 7.25-7.1 (m,4H), 7.55 (m,1H), 7.75 (m,1H), 8.2 (d,1H), 8.60 (s,1H), 9.2 (t,1H), 12.7 (s,1H)

20 M.P. = 179 °C

HPLC 95.6 %

Example 116 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide

25 **Step 1 Methyl 2,4-dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of the Step 4 of Example 15 using the compound obtained in the Step 2 of the Example 20

Step 2 2,4-Dioxo-1-methyl-3-(pyridine-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1

5 Step 3 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide

To a stirred solution of 0.2 g (0.65 mmol) of compound obtained in the preceding Step 2 in 7 ml of dichloromethane are added 0.113 g (0.65 mmol) of EDCI, 0.080 g (0.65 mmol) of HOBT and 0.064 g (0.660 ml, 0.65 mmol) of 3,4-methylenedioxy-benzylamine. After 20
10 hours of stirring at room temperature and an usual treatment, 0.140 g (yield: 48%) of the desired product are obtained.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.0 (s, 2H), 6.80-6.95 (m, 3H), 7.25-7.35 (m, 2H), 7.55-7.60 (m, 1H), 8.25-8.35 (m, 1H), 8.45-8.50 (m, 2H), 8.65
15 (s, 1H), 9.20 (t, 1H)

IR 3265, 1707, 1663, 1618, 1501, 1490, 1254, 1037, 925 cm^{-1}

M.P. = 161 $^{\circ}\text{C}$

HPLC 94.6 %

20 Example 117 : 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Step 2 of the Example 116 and 4-methoxy-benzylamine. 0.280 g (yield: 25%) of the desired product is isolated after a chromatography over silica gel.

25 TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 3.70 (s, 3H), 4.40 (d, 2H), 5.15 (s, 2H), 6.80 (d, 2H), 7.2-7.3 (m, 4H), 7.55-7.60 (m, 1H), 8.25-8.30 (m, 1H), 8.45 (d, 2H), 8.60 (s, 1H), 9.20 (m, 1H)

IR 3231, 1706, 1657, 1625, 1505, 1324, 1248, 1039, 827 cm^{-1}

M.P. = 180.7 °C

HPLC 94.3 %

5

Example 118 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide

10

To a stirred solution of 0.280 g (0.67 mmol) of compound of the Example 117 in 20 ml of dichloromethane, maintained at 0°C, are added, under an inert atmosphere, 1.7 g (0.63 ml, 6.7 mmol) of BBR_3 in 2 ml of dichloromethane. After 20 minutes of stirring at room temperature, the reaction mixture is poured on a saturated solution of NaHCO_3 , decanted, and extracted. The organic phase is dried and concentrated under vacuum to provide 0.150 g (yield 53.4%) of the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.60

15

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.70 (d, 2H), 7.15 (d, 2H), 7.3 (d, 2H), 7.55-7.60 (m, 1H), 8.30 (d, 1H), 8.50 (d, 2H), 8.65 (s, 1H), 9.20 (m, 1H), 9.30 (s, 1H)

IR 3388, 1701, 1656, 1639, 1615, 1508, 1251, 830, 772, 751 cm^{-1}

M.P. = 137.7 °C

HPLC = 91.1 %

20

Example 119 Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

Step 1 Benzyl 3-(4-methoxycarbonyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

25

The compound is obtained according to the procedure of Step 1-5 to Step 2-5 of the Preparation B using, in Step 1-5, 4-amino-isophthalic acid 1-benzylester 3-methyl ester and methyl 4-aminomethyl benzoate. The desired product is purified by reflux in methanol.

TC. CH_2Cl_2 / MeOH 95/5 R_f = 0.65

NMR. DMSO ^1H δ (ppm) 3.8 (s, 3H), 5.10 (s, 2H), 5.35 (s, 2H), 7.20-7.80 (m, 8H), 7.80-7.90 (m, 2H), 8.20-8.30 (m, 1H), 8.50 (s, 1H), 11.90 (s, 1H)

HPLC 97.0 %

Step 2 Benzyl 3-(4-methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the preceding Step 1

TLC CH_2Cl_2 / MeOH 95/5 $R_f = 0.65$

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 3.80 (s, 3H), 5.20 (s, 2H), 5.35 (s, 2H), 7.30-7.60 (m, 8H), 7.80-7.90 (m, 2H), 8.20-8.30 (m, 1H), 8.60 (s, 1H)

HPLC 97.0 %

Step 3 3-(4-Methoxycarbonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid

To a stirred solution of 10.8 g (23.6 mmol) of the compound obtained in the preceding Step 2 in 120 ml of dichloromethane and 80 ml of methanol, are added 3.2 g of Pd/C at 10%. The reaction mixture is stirred under hydrogen atmosphere for 1 hour at room temperature, followed by filtration over Celite. The filtrate is concentrated under vacuum to give a first crystallized crop. The insoluble part is extracted three times by a mixture of methanol/water/saturated solution of NaHCO_3 . The organic phases are gathered and acidified to pH 1 by a concentrated solution of chlorhydric acid, to give to a second crop corresponding to the desired product. The two crops are put together and dried under vacuum to provide 6.9 g of the desired product (yield 79%)

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 3.80 (s, 3H), 5.20 (s, 2H), 7.40 (dd, 2H), 7.60 (dd, 1H), 7.90 (dd, 2H), 8.30 (dd, 1H), 8.60 (s, 1H), 13.20 (bs, 1H)

HPLC > 97.0 %

Step 4 Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 3-methoxy-benzylamine

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.70 (s,3H), 3.80 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 6.80 (d,1H), 6.90 (m,2H), 7.25 (m,1H), 7.45 (d,2H), 7.55 (d,1H), 7.85 (d,2H), 8.25 (d,1H), 8.60 (s,1H), 9.25 (t,1H)

IR 3435, 2361, 1716, 1703, 1666, 1617, 1498, 1455, 1282, 1125, 839, 749, cm^{-1}

5 M.P. = 199.0°C

HPLC 98.6 %

Example 120 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

10 The compound is obtained by hydrolysis of compound of the Example 119 using as reagent K_2CO_3 in a mixture of methanol and water under reflux for 8 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.40

15 NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 6.80 (d,1H), 6.90 (m,2H), 7.25 (t,1H), 7.45 (d,2H), 7.55 (d,1H), 7.85 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.25 (t,1H), 12.85 (bs,1H)

IR 3395, 2345, 1719, 1647, 1616, 1501, 1310, 1238, 1052, 839, 781, 751 cm^{-1}

M.P. = 279.0°C

HPLC 97.4 %

20 **Example 121 Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-methylthio-benzylamine

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

25 NMR. DMSO ^1H δ (ppm) 2.45 (s,3H), 3.55 (s,3H), 3.80 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 7.20 (m,4H), 7.45 (d,2H), 7.55 (s,1H), 7.90 (d,2H), 8.25 (d,1H), 8.60 (s,1H), 9.20 (t,1H)

IR 3395, 1708, 1656, 1641, 1508, 1479, 1330, 1280, 1254, 1117, 783, 749, cm^{-1}

MP = 172 °C

HPLC 99.2 %

Example 122 4-[1-Methyl-6-(4-methylsulfonyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

- 5 The compound is obtained by hydrolysis of compound of the Example 121 using as reagent K_2CO_3 in a mixture of methanol and water under reflux for 48 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.35

- 10 NMR DMSO ^1H δ (ppm) 2.45 (s, 3H), 3.55 (s, 3H), 4.45 (d, 2H), 5.20 (s, 2H), 7.25 (m, 4H), 7.40 (d, 2H), 7.55 (d, 1H), 7.85 (d, 2H), 8.25 (d, 1H), 8.60 (s, 1H), 9.25 (t, 1H), 12.85 (bs, 1H),
IR 1705, 1656, 1642, 1616, 1479, 1330, 1247, 1101, 1020, 760, 751 cm^{-1}

MP = 171 °C

HPLC 98.0 %

- 15 **Example 123 Methyl 4-[1-methyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and 4-trifluoromethoxy-benzylamine.

- 20 TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.35

NMR DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.80 (s, 3H), 4.50 (d, 2H), 5.20 (s, 2H), 7.30 (d, 2H), 7.35-7.50 (m, 4H), 7.55 (d, 1H), 7.90 (d, 2H), 8.25 (d, 1H), 8.65 (s, 1H), 9.30 (t, 1H)

IR 1712, 1656, 1639, 1506, 1274, 1156, 1104, 751 cm^{-1}

MP = 212 °C

- 25 HPLC 99.6 %

Example 124 Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

655

129

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 3 and 4-fluorobenzylamine.

TLC CH_2Cl_2 / MeOH 95/5 $R_f = 0.45$

5 NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 3.80 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 7.10-7.20 (m,2H), 7.30-7.40 (m,2H), 7.40-7.50 (d,2H), 7.55 (d,1H), 7.85 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.25 (t,1H)

IR 1709, 1657, 1618, 1499, 1264, 768, 749, 716 cm^{-1}

M.P. = 198 °C

HPLC 98.2 %

10 **Example 125 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 124

TLC CH_2Cl_2 / MeOH 95/5 $R_f = 0.25$

15 NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 7.10-7.20 (m,2H), 7.30-7.40 (m,2H), 7.45 (d,2H), 7.55 (d,1H), 7.90 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.25 (t,1H), 12.90 (bs,1H)

IR 3661, 2765, 1710, 1649, 1617, 1505, 1224, 829, 752 cm^{-1}

M.P. = 272 °C

20 HPLC 98.0 %

Example 126 Methyl 4-[6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

25 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the Step 3 of Example 119 and C-benzofurazan-5-yl-methylamine, which is obtained from 5-bromomethyl-benzofurazan by reaction in a first step with sodium diformylamide in acetonitrile at 70°C overnight, and in a second step by a treatment for 2 hours under reflux to a solution of ethanol/HCl 5%

TLC CH_2Cl_2 / MeOH 95/5 $R_f = 0.70$

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.85 (s,3H), 4.65 (d,2H), 5.25 (s,2H), 7.45 (d,2H), 7.60 (d,2H), 7.90 (m,3H), 8.00 (d,1H), 8.30 (d,1H), 8.65 (s,1H), 9.40 (t,1H)

IR 3257, 1731, 1702, 1659, 1619, 1506, 1419, 1281, 1109, 877, 769, 751 cm^{-1}

M.P = 234 °C

5 HPLC 98.6 %

Example 127 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 126. After acidification, the precipitate is
10 filtered off

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.35

NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 4.60 (d,2H), 5.20 (s,2H), 7.40 (d,2H), 7.60 (d,2H), 7.85 (d,3H), 8.00 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.40 (t,1H), 12.9 (bs,1H)

IR 3249, 1708, 1662, 1617, 1479, 1427, 1322, 1250, 1008, 879, 790, 754 cm^{-1}

15 M.P = 276 °C

HPLC 97.6 %

Example 128 Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate
20

Step 1 4-Amino-isophthalic acid 3-methyl ester

The compound is obtained according to the procedure of the Step 3 of the Example 119 using as substrate 4-amino-isophthalic acid 1-benzylester 3-methyl ester

Step 2 6-Amino-N-(4-methoxy-benzyl)-isophthalamide acid methyl ester

25 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxy-benzylamine.

Step 3 Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-

65b

quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 1-5 to 2-5 of the Preparation B using in the Step 1-5 the compound obtained in the preceding Step 2 and methyl 4-aminomethyl benzoate

5 TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.55

NMR. DMSO ¹H δ (ppm) 3.70 (s,3H), 3.80 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 6.90 (d,2H), 7.20 (m,3H), 7.45 (d,2H), 7.90 (d,2H), 8.15 (d,1H), 8.50 (s,1H), 9.15 (t,1H), 11.8 (s,1H)

IR 3265, 2935, 2553, 1719, 1665, 1637, 1514, 1459, 1275, 1105, 827, 751 cm⁻¹

M.P. = 287.5 °C

10 HPLC 98.3 %

Example 129 Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained the Example 128 and iodomethane in DMF with K₂CO₃. The

15 desired compound crystallizes in a mixture of dichloromethane/ether

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.55

NMR. DMSO ¹H δ (ppm) 1.25 (t,3H), 3.75 (s,3H), 3.85 (s,3H), 4.20 (d,2H), 4.40 (d,2H), 5.25 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.45 (d,2H), 7.60 (d,1H), 7.90 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

20 IR 3403, 2361, 1708, 1659, 1646, 1615, 1508, 1273, 1251, 1113, 847, 758 cm⁻¹

M.P. = 190 °C

HPLC 96.9 %

Example 130 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

25 The compound is obtained by hydrolysis of compound of the Example 112 using as reagent K₂CO₃ in a mixture of methanol and water under reflux for 3 hours. After acidification of the reaction mixture, the precipitate obtained is filtered off to provide the desired product.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.45$

NMR DMSO ^1H δ (ppm) 1.25 (t, 3H), 3.70 (s, 3H), 4.20 (q, 2H), 4.40 (d, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.40 (d, 2H), 7.60 (d, 1H), 7.85 (d, 2H), 8.25 (d, 1H), 8.65 (s, 1H), 9.20 (t, 1H), 12.85 (bs, 1H)

5 IR 2361, 1708, 1655, 1616, 1501, 1466, 1322, 1250, 1177, 1032, 823, 754 cm^{-1}

M.P. = 160 °C

HPLC 98.2 %

Example 131 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

10 **Step 1 Methyl 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylate**

The compound is obtained according to the procedure of the Step 4 of the Example 15 using the compound obtained in the Step 1 of example 16

15 **Step 2 3-(4-methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid**

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the preceding Step 1

Step 3 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

20 The compound is obtained (0.160 g, yield 63%) according to the procedure of the Step 3 of the Example 116 using the compound obtained in the preceding Step 2 and 4-(aminomethyl)pyridine

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

25 NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.7 (s, 3H), 4.5 (d, 2H), 5.10 (s, 2H), 6.80-6.90 (m, 2H), 7.30-7.35 (m, 4H), 7.55-7.60 (m, 1H), 8.25-8.30 (m, 1H), 8.38-8.42 (m, 2H), 8.70 (s, 1H), 9.35 (t, 1H)

IR 3269, 1705, 1659, 1644, 1615, 1510, 1245, 1180, 842, 785 cm^{-1}

M.P. = 213.9 °C

657

HPLC 97.8 %

Example 132 3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

To a stirred solution of 0.630 g (1.46 mmol) of compound of the Example 131 in 50 ml of dichloromethane are added, under an inert atmosphere, 3.7 g (13 ml, 14.6 mmol) of BBr₃ in 5 ml of dichloromethane. After 1 hour of stirring at room temperature, the reaction mixture is cooled and poured on 100 ml of a saturated solution of NaHCO₃. The precipitate obtained is purified by chromatography over silica gel (gradient of methanol in dichloromethane) and solidified in dichloromethane to provide the desired compound.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.50NMR DMSO ¹H δ (ppm) 3.45 (s, 3H), 4.45 (d, 2H), 5.0 (s, 2H), 6.60 (d, 2H), 7.1 (d, 2H), 7.25 (d, 2H), 7.5 (d, 1H), 8.20 (d, 1H), 8.40 (d, 2H), 8.60 (s, 1H), 9.20 (s, 1H), 9.20 (t, 1H)IR 3048, 1705, 1659, 1642, 1507, 1479, 1328, 1244, 831 cm⁻¹

M.P. = 262.0 °C

HPLC 94.8 %

Example 133 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

The compound is obtained according to the procedure of the Example 33 using the same substrate and 4-picolylamine in the step of amidification.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.25NMR DMSO ¹H δ (ppm) 3.45 (s, 3H), 4.5 (d, 2H), 7.3 (d, 2H), 7.55 (d, 1H), 8.25 (d, 1H), 8.5 (d, 2H), 8.6 (s, 1H), 9.35 (t, 1H), 11.7 (s, 1H)IR 3185, 1686, 1618, 1479, 1417, 1326, 782 cm⁻¹

M.P. = 292 °C

HPLC 96.4 %

Step 2 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and α -bromo-*para*-toluonitrile

5 TLC AcOEt Rf = 0.55

NMR. CDCl₃ ¹H δ (ppm) 3.60 (s, 3H), 4.60 (d, 2H), 5.30 (s, 2H), 7.3 (m, 3H), 7.60 (s, 4H), 8.40 (m, 1H), 8.45 (m, 2H), 8.65 (m, 1H), 8.80 (s, 1H)

M.P. = 258°C

HPLC 98.9 %

10 **Example 134 1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and 4-(3-chloro-propenyl)-pyridine hydrochloride.

15 TLC CH₂Cl₂ / MeOH 90/10 Rf = 0.50

NMR DMSO ¹H δ (ppm) 3.60 (s, 3H), 4.50 (m, 2H), 4.80 (m, 2H), 6.50 (m, 1H), 6.65 (m, 1H), 7.3 (m, 2H), 7.40 (m, 2H), 7.60 (d, 1H), 8.25 (d, 1H), 8.50 (m, 4H), 8.65 (s, 1H), 9.35 (m, 1H)

M.P. = 117°C

20 HPLC 99.5 %

Example 135 Methyl 4-[1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl-4-(bromomethyl)-benzoate.

25

TLC CH₂Cl₂ / MeOH 90/10 Rf = 0.45

660
658

135

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 3.80 (s,3H), 4.5 (d,2H), 5.20 (s,2H), 7.3 (m,2H), 7.45 (d,2H), 7.60 (d,1H), 7.90 (m,2H), 8.25 (d,1H), 8.5 (m,2H), 8.65 (s,1H), 9.35 (t,1H)

IR 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751 cm^{-1}

M.P. = 236 $^{\circ}\text{C}$

5 HPLC 97.5 %

Example 136 4-[1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound obtained in the Example 135. The corresponding hydrochloride is obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

10 NMR. DMSO ^1H δ (ppm) 2.4-4.40 (m,1H), 3.60 (s,3H), 4.15 (t,2H), 5.20 (s,2H), 7.40 (d,2H), 7.60 (d,1H), 7.90 (m,4H), 8.30 (d,1H), 8.70 (s,1H), 8.80 (d,1H), 9.65 (t,1H), 12.9 (bs,1H)

15 IR 3265, 1718, 1704, 1663, 1641, 1318, 1289, 1113, 751 cm^{-1}

M.P. = 268 $^{\circ}\text{C}$

HPLC 97.9 %

Example 137 Methyl (4-[1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl)-acetate

20 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of Example 133 and methyl 4-(bromomethyl-phenyl) acetate.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.45

25 NMR. DMSO ^1H δ (ppm) 3.50-3.60 (s,6H), 3.65 (s,2H), 4.5 (t,2H), 5.15 (s,2H), 7.20 (m,2H), 7.20-7.35 (m,4H), 7.55 (d,1H), 8.25 (d,1H), 8.5 (d,2H), 8.65 (s,1H), 9.35 (t,1H)

IR 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751 cm^{-1}

M.P. = 141 $^{\circ}\text{C}$

HPLC 96.4 %

Example 138 (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 137. The corresponding hydrochloride is obtained after dissolution of the compound in a hot solution of isopropanol/ HCl 0.1 M. The desired compound is purified by crystallization from acetonitrile.

NMR. DMSO ^1H δ (ppm) 2.50-5.50 (br, HCl+OH), 3.45-3.60 (2s, 5H), 4.70 (d, 2H), 5.15 (s, 2H), 7.15 (d, 2H), 7.25 (d, 2H), 7.55 (d, 1H), 7.85 (d, 2H), 8.30 (d, 1H), 8.65 (s, 1H), 8.75 (d, 2H), 9.55 (t, 1H).

IR 3298, 1736, 1707, 1663, 1631, 1505, 1473, 1320, 1157, 751 cm^{-1}

M.P. = 241 °C

HPLC 97.5 %

Example 139 Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate

To a stirred suspension of 0.500 g (1.10 mmol) of compound of the Example 135 in 20 ml of dichloromethane, maintained at -20°C, are added 0.250 g (1.10 mmol) of *meta*-chloroperbenzoic acid in 5 ml of dichloromethane. After stirring overnight at room temperature, the reaction mixture is washed successively with a saturated solution of Na_2CO_3 and water. The organic phase is dried and concentrated under vacuum. A chromatography over silica gel (gradient of methanol in dichloromethane) followed by a solidification in dichloromethane/ether provides 0.300 g (yield 57%) of the desired product.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.28

NMR. DMSO ^1H δ (ppm) 3.55 (s, 3H), 3.85 (s, 3H), 4.45 (d, 2H), 5.25 (s, 2H), 7.3 (d, 2H), 7.45 (d, 2H), 7.60 (d, 1H), 7.90 (d, 2H), 8.15 (d, 2H), 8.30 (s, 1H), 8.65 (s, 1H), 9.35 (t, 1H).

IR 1705, 1655, 1617, 1478, 1283, 750, 711 cm^{-1}

M.P. = 218 °C

HPLC 99.1 %

Example 140 4-{1-Methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 139

NMR. DMSO ^1H δ (ppm) 3.55 (s,3H), 4.55 (d,2H), 5.20 (s,2H), 7.30-7.50 (m,4H), 7.60 (d,1H), 7.85 (d,2H), 8.25 (d,2H), 8.30 (d,1H), 8.65 (s,1H), 9.35 (t,1H), 12.9 (bs,1H)

IR 1702, 1655, 1617, 1479, 1245, 753 cm^{-1}

M.P. = 192 °C

HPLC 98.4 %

Example 141 Methyl{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-1-yl}-acetate

The compound is obtained by alkylation of the compound of Example 3 using K_2CO_3 and methylbromoacetate in DMF

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 3.70 (s,3H), 4.40 (d,2H), 5.05 (s,2H), 5.15 (s,2H), 6.0 (s,2H), 6.85 (m,3H), 7.30 (m,5H), 7.55 (d,1H), 8.20 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

IR 3282, 2361, 1736, 1669, 1632, 1464, 1370, 1236, 1040, 833, 776, 758 cm^{-1}

M.P. = 194.0 °C

HPLC 97.6 %

Example 142 {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl}-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 141

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 4.35 (d,2H), 4.90 (s,2H), 5.15 (s,2H), 5.95 (s,2H), 6.80 (m,3H), 7.30 (m,5H), 7.50 (d,1H), 8.20 (d,1H), 8.60 (s,1H), 9.20 (t,1H), 13.25 (bs,1H)

IR 3346, 2935, 1709, 1668, 1612, 1499, 1467, 1305, 1250, 1117, 1036, 873 cm^{-1}

M.P. = 163.0 $^{\circ}\text{C}$

5 HPLC 99.6 %

Example 143 Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate

The compound is obtained according to the procedure of the Step 2 of the Example 34 using the compound obtained in the Example 37 and methyl 4-(bromomethyl)-benzoate.

10 TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.90 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.0 (s,2H), 6.80-6.95 (m,3H), 7.45 (d,2H), 7.60 (d,1H), 7.85 (d,2H), 8.30 (d,1H), 8.65 (s,1H), 9.20 (t,1H)

IR 3418, 1713, 1666, 1657, 1617, 1497, 1477, 1280, 1252, 1038, 770, 749 cm^{-1}

15 M.P. = 233.5 $^{\circ}\text{C}$

HPLC 99.6 %

Example 144 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid

20 The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound obtained in the Example 143

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.40 |

NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 5.95 (s,2H), 6.80-6.95 (m,3H), 7.40 (d,2H), 7.60 (d,1H), 7.85 (d,2H), 8.30 (d,1H), 8.60 (s,1H), 9.20 (t,1H), 12.85 (s,1H)

IR 3377, 3233, 1717, 1698, 1665, 1649, 1502, 1481, 1236, 751 cm^{-1}

M.P. = 295.7 $^{\circ}\text{C}$

25 HPLC 97.9 %

660

Example 145 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-sulfamoyl-benzylamide

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C and 4-(aminomethyl)benzene sulfonamide hydrochloride hydrate.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.37$

NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 4.55 (d, 2H), 5.15 (s, 2H), 7.2-7.35 (m, 7H), 7.50 (d, 2H), 7.60 (d, 1H), 7.80 (d, 2H), 8.30 (d, 1H), 8.65 (s, 1H), 9.35 (t, 1H)

IR 3290, 1709, 1652, 1618, 1503, 1321, 1154, 702 cm^{-1}

M.P. = 266 °C

HPLC 97.5 %

Example 146 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid [3-(pyridin-4-ylsulfanyl)-propyl]-amide

The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 3-(pyridin-4-ylsulfanyl)-propylamine and dichloromethane as solvent. (The reactant 3-(pyridin-4-ylsulfanyl)-propylamine is obtained according to the method described in *Bioorg Med Chem*, 1996, 4, 557-562)

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

NMR. DMSO ^1H δ (ppm) 1.8-1.90 (m, 2H), 3.1-3.20 (m, 2H), 3.4-3.50 (m, 2H), 3.60 (s, 3H), 5.20 (s, 2H), 7.2-7.40 (m, 7H), 7.50-7.55 (m, 1H), 8.20 (d, 1H), 8.30-8.40 (m, 2H), 8.60 (s, 1H), 8.80 (t, 1H)

IR 3308, 1705, 1662, 1636, 1578, 1509, 1447, 1321, 804, 712 cm^{-1}

M.P. = 130.7 °C

HPLC 99.2 %

Example 147 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (4-morpholin-4-yl-butyl)-amide

The compound is obtained according to the procedure of the Step 3 of Example 116 using the compound obtained in the Preparation C, 4-morpholin-4-yl-butylamine, and dichloromethane as solvent. (The reactant 4-morpholin-4-yl-butylamine is obtained according to the method described in *J Med. Chem*, 1997, 40, 3915-3925)

5 TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.60

NMR DMSO ¹H δ (ppm) 1.4-1.60 (m, 4H), 2.2-2.35 (m, 6H), 3.20-3.35 (m, 2H), 3.55 (s, 3H), 3.5-3.60 (m, 4H), 5.20 (s, 2H), 7.2-7.35 (m, 5H), 7.50 (d, 1H), 8.20-8.25 (m, 1H), 8.60 (s, 1H), 8.70 (t, 1H)

IR 3402, 2942, 1707, 1645, 1476, 1327, 1118, 763 cm⁻¹

10 M.P. = 170.6 °C

HPLC 99.3 %

Example 148 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-benzyl-piperidin-4-yl)-amide

15 The compound is obtained according to the procedure of the Example 9 using the compound obtained in the Preparation C, 4-amino-1-benzylpiperidine, and dichloromethane as solvent. The desired compound crystallizes from a mixture of dichloromethane and ether

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.50

20 NMR DMSO ¹H δ (ppm) 1.60 (m, 2H), 1.75 (m, 2H), 2.0 (t, 2H), 2.8 (d, 2H), 3.45 (s, 2H), 3.55 (s, 3H), 3.75 (m, 1H), 5.15 (s, 2H), 7.30 (m, 10H), 7.55 (d, 1H), 8.20 (d, 1H), 8.50 (d, 1H), 8.60 (s, 1H)

IR 3257, 2943, 2749, 1709, 1656, 1633, 1511, 1332, 1242, 1077, 829, 750 cm⁻¹

M.P. = 219.4 °C

HPLC 98.6 %

25 **Example 149 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide**

To a round bottom protected from moisture and under inert atmosphere are introduced 1.9 g (4.4 mmol) of compound of Example 13 in 200 ml of dichloromethane. To the stirred

solution are added dropwise 4.2 ml (11.1 g, 44 mmol) of BBr_3 in 17 ml of dichloromethane. After 30 minutes at room temperature the reaction mixture is poured to a 500 ml saturated solution of NaHCO_3 , extracted with dichloromethane, dried and concentrated under vacuum. A crystallization of the crude product in methanol/ether provides 1.35 g (yield 74%) of the desired compound.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.55$

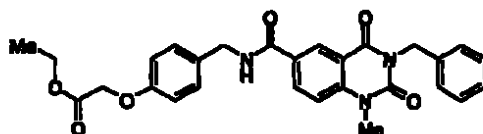
NMR. DMSO ^1H δ (ppm) 3.60 (s, 3H), 4.40 (d, 2H), 5.20 (s, 2H), 6.7-6.75 (m, 2H), 7.10-7.20 (m, 2H), 7.2-7.40 (m, 5H), 7.55 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H), 9.20 (t, 1H), 9.0-9.3 (bs, 1H)

IR 3314, 1698, 1635, 1622, 1500, 1480, 1453, 1255, 826, 748 cm^{-1}

MP = 191.8 °C

HPLC 96.4 %

Example 150 Ethyl (4-[[[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl]-phenoxy)-acetate



To a round bottom protected from moisture and under inert atmosphere are introduced 0.45 g (1.08 mmol) of compound of Example 149 in 13.5 ml of DMF. To the stirred solution are added 0.3 g of K_2CO_3 (2.16 mmol) and 0.24 ml (2.016 mmol) of ethyl bromoacetate. After 1 hour at 60 °C the reaction mixture is concentrated under vacuum. The crude product is taken up in dichloromethane, washed with water, dried and concentrated under vacuum to provide 0.410 g (yield 75.8%) of the desired compound.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

NMR. DMSO ^1H δ (ppm) 1.2 (t, 3H), 3.60 (s, 3H), 4.15 (q, 2H), 4.45 (d, 2H), 4.80 (s, 2H), 5.20 (s, 2H), 6.90 (d, 2H), 7.2-7.40 (m, 7H), 7.5 (d, 1H), 8.20 (d, 1H), 8.60 (s, 1H), 9.20 (t, 1H)

IR 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750 cm^{-1}

MP = 172.6 °C

HPLC 97.8 %

Example 151 (4-[[[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-

carbonyl)-amino]-methyl)-phenoxy)-acetic acid

The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 150

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

5 NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 4.40 (d,2H), 4.65 (s,2H), 5.15 (s,2H), 6.85 (d,2H), 7.2-7.40 (m,7H), 7.55 (d,1H), 8.25 (d,1H), 8.65 (s,1H), 9.20 (t,1H), 12.95 (bs,1H)

IR 3407, 1755, 1705, 1642, 1508, 1324, 1210, 750 cm^{-1}

M.P = 195.6 °C

HPLC 98.3 %

10 **Example 152 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoylmethoxy-benzylamide**

The compound is obtained according to the procedure of the Example 1 using the compound of Example 151 and dimethylamine 2M in solution in THF

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

15 NMR. DMSO ^1H δ (ppm) 2.80 (s,3H), 3.0 (s,3H), 3.55 (s,3H), 4.40 (d,2H), 4.80 (s,2H), 5.20 (s,2H), 6.90 (d,2H), 7.2-7.40 (m,7H), 7.50 (d,1H), 8.20 (d,1H), 8.65 (s,1H), 9.25 (t,1H)

IR 3276, 1704, 1659, 1635, 1499, 1317, 1240, 1066, 750 cm^{-1}

M.P = 152.7 °C

20 HPLC 96.5 %

Example 153 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (3-phenyl-allyl)-amide

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 3-phenyl-allylamine hydrochloride.

25 TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.80$

NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 4.10 (m,2H), 5.20 (s,2H), 6.35 (m,1H), 6.60 (m,1H), 7.20-7.35 (m,8H), 7.40 (m,2H), 7.55 (d,1H), 8.30 (d,1H), 8.70 (s,1H), 9.00 (m,1H)

M.P = 193.0 °C

5 HPLC 99.7 %

Example 154 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-cyano-benzylamide

The compound is obtained according to the procedure of the Example 9 using the compound of the Preparation C and 4-amino-benzyl benzonitrile. The desired product is solidified in a mixture of dichloromethane/ether

10

TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.46

NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 4.60 (d,2H), 5.15 (s,2H), 7.20-7.40 (m,5H), 7.45-7.60 (m,3H), 7.80 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.40 (t,1H)

IR 3305, 2224, 1708, 1664, 1638, 1507, 1318, 751 cm^{-1}

15 M.P = 245.0 °C

HPLC 96.2 %

Example 155 4-[[[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl]-benzoic acid

20 The compound is obtained according to the procedure of the Step 2-4 of the Preparation B using the compound of the Example 11

TLC CH_2Cl_2 / MeOH 90/10 Rf = 0.30

NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 4.55 (d,2H), 5.15 (s,2H), 7.25 (m,5H), 7.40 (d,2H), 7.55 (d,1H), 7.90 (d,2H), 8.25 (d,1H), 8.65 (s,1H), 9.30 (t,1H), 12.90 (bs,1H)

25 IR 3395, 1707, 1698, 1642, 1618, 1501, 1431, 1291, 1242, 938, 829, 759 cm^{-1}

M.P = 228.5 °C

HPLC 96.9 %

Example 156 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-dimethylcarbamoyl-benzylamide

The compound is obtained according to the procedure of the Example 1 using the compound of the Example 155 and dimethylamine in solution 2M in THF

5 TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.70$

NMR. DMSO ^1H δ (ppm) 3.0 (m, 6H), 3.55 (s, 3H), 4.55 (d, 2H), 5.15 (s, 2H), 7.30 (m, 9H), 7.60 (d, 1H), 8.30 (d, 1H), 8.65 (s, 1H), 9.30 (t, 1H)

IR 3249, 2361, 1705, 1657, 1609, 1504, 1452, 1254, 1069, 1020, 839, 750 cm^{-1}

M.P. = 194.7 °C

10 HPLC 96.8 %

Example 157 3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the Step 1-5 to 3-5 of the preparation B using in the Step 1-5 4-dimethylamino-benzyl isocyanate, and then according to the procedure of Example 1 using the compound obtained in the preceding step and 4-methoxy-benzylamine

15 NMR. DMSO ^1H δ (ppm) 2.80 (s, 6H), 3.70 (s, 3H), 4.40 (d, 2H), 4.95 (s, 2H), 6.60 (d, 2H), 6.85 (d, 2H), 7.15-7.25 (m, 5H), 8.10 (dd, 1H), 8.50 (s, 1H), 9.10 (t, 1H), 11.7 (s, 1H)

IR 3177, 1729, 1630, 1512, 1445, 1249, 765 cm^{-1}

20 M.P. = 267 °C

HPLC 98.5%

Example 158 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

25 The compound is obtained according to the procedure of the Example 97 using as substrates the compound obtained in the Example 95 and 2.5 equivalents of methanesulfonyl chloride

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.22$

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NMR DMSO ^1H δ (ppm) 2.90 (s,3H), 3.55 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.10 (s,2H), 6.90 (d,2H), 7.10 (d,2H), 7.25 (d,2H), 7.30 (d,2H), 7.55 (s,1H), 8.25 (d,1H), 8.60 (s,1H), 9.2 (t,1H), 9.70 (s,1H)

IR 1655, 1615, 1513, 1500, 1325, 1248, 1148 cm^{-1}

5 MP = 224 °C

HPLC 98.8 %

Example 159 *tert*-Butyl {5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 1 of the Example 34 and *tert*-butyl (5-bromomethyl-pyridin-2-yl)-carbamate

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.80

15 NMR DMSO ^1H δ (ppm) 1.45 (s,9H), 3.55 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 5.10 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,1H), 7.70 (m,2H), 8.25-8.30 (m,2H), 8.65 (s,1H), 9.2 (t,1H), 9.70 (s,1H)

IR 1711, 1654, 1614, 1508, 1478, 1302, 1243, 1159 cm^{-1}

MP = 204 °C

HPLC 99.3 %

20 **Example 160** 3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained by deprotection of compound of the Example 159 by using trifluoroacetic acid in dichloromethane

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.40

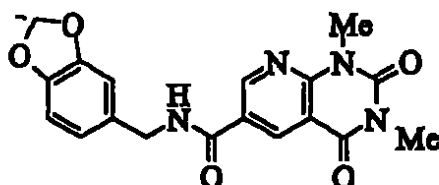
25 NMR DMSO ^1H δ (ppm) 3.55 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 4.95 (s,2H), 5.80 (bs,2H), 6.35 (d,1H), 6.90 (d,2H), 7.25 (d,2H), 7.40 (dd,1H), 7.50 (d,1H), 7.95 (s,1H), 8.25 (dd,1H), 8.60 (s,1H), 9.2 (t,1H)

IR 1704, 1648, 1615, 1509, 1477, 1245 cm^{-1}

MP = 155 °C

HPLC 99.5 %

Example 161 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



5 **Step 1** 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid

The compound is obtained by hydrolysis in a mixture of dioxan/water of ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylate (*Heterocycles* 1998, 48(12),2521-2528) in presence of LiOH.

10 TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.10

R.M.N. DMSO ¹H δ (ppm) 3.30 (s,3H), 3.60 (s,3H), 8.70 (s,1H), 9.15 (s,1H), 13.5 (bs,1H)

Step 2 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

15 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.90

NMR. DMSO ¹H δ (ppm) 3.35 (s,3H), 3.6 (s,3H), 4.40 (d,2H), 6.0 (s,2H), 6.75-6.85 (m,2H), 6.90 (s,1H), 8.80 (s,1H), 9.15 (s,1H); 9.30 (t,1H)

20 IR 3227, 1705, 1663, 1632, 1608, 1498, 1299, 1250, 1040, 794 cm⁻¹

M.P = 218 °C

HPLC 94.6 %

Example 162 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

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Step 1 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid

The compound is obtained by hydrolysis in a mixture of dioxan/water of methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylate

5 (Heterocycles 1994, 37(1), 563-570) in presence of LiOH

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.01

NMR. DMSO ¹H δ (ppm) 3.30 (s, 3H), 3.60 (s, 3H), 8.40 (s, 1H), 9.00 (s, 1H), 13.3 (bs, 1H)

Step 2 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

10 The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and piperonylamine.

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.90

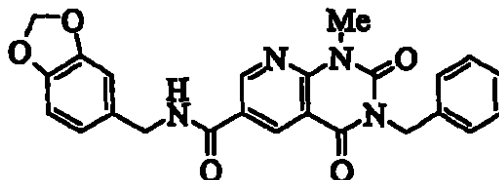
NMR DMSO ¹H δ (ppm) 3.35 (s, 3H), 3.65 (s, 3H), 4.45 (d, 2H), 6.0 (s, 2H), 6.80-6.90 (m, 2H), 6.95 (s, 1H), 8.50 (s, 1H), 8.95 (s, 1H), 9.25 (t, 1H)

15 IR 3379, 1713, 1662, 1478, 1253, 1238, 924, 750 cm⁻¹

M.P. = 288 °C

HPLC 96.3 %

Example 163 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide



20

Step 1 N'-(1-Benzyl-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-N,N-dimethyl-formamidine

0.56 g (2.5 mmol) of 6-amino-3-benzyl-1H-pyrimidine-2,4-dione (Tetrahedron Letters, 1991, 32(45), 6534-6540) in 20 ml of DMF are stirred under inert atmosphere. 1 ml (7.5 mmol) of *NN'*-dimethylformamide dimethyl acetal is added to this solution and the mixture is heated to reflux for 20 minutes. After cooling and concentration under vacuum, the residue is taken up in dichloromethane, and the organic phase is washed with water,

25

dried over Na_2SO_4 , and concentrated under vacuum until a low volume. Then the crude product is precipitate by addition of ether. After filtration 0.680 g (yield 72.6%) of the desired compound is obtained.

TLC CH_2Cl_2 / MeOH 90/10 $R_f = 0.80$

5 NMR. DMSO ^1H δ (ppm) 3.0 (s, 3H), 3.15 (s, 3H), 3.30 (s, 3H), 4.90 (s, 2H), 5.20 (s, 1H), 7.2-7.35 (m, 5H), 8.10 (s, 1H)

Step 2 *N*-(1-Benzyl-5-iodo-3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl)-*N,N*-dimethyl-formamidine

10 To a stirred solution of 0.68 g (2.38 mmol) of the compound obtained in the preceding Step 1 in 24 ml of anhydrous dichloromethane is added 0.64 g (2.85 mmol) of *N*-iodosuccinimide. After 30 minutes of reflux, the reaction mixture is cooled and the organic phase is washed with water, dried over Na_2SO_4 , and concentrated under vacuum. The crude product is precipitated in ether to obtain 0.680 g (yield 69.3%) of the desired compound.

15 NMR CDCl_3 ^1H δ (ppm) 3.05 (s, 3H), 3.15 (s, 3H), 3.40 (s, 3H), 5.20 (s, 2H), 7.2-7.30 (m, 3H), 7.5-7.55 (m, 2H), 7.7 (s, 1H)

M.P. = 186.3°C

Step 3 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid ethyl ester

20 To a stirred solution of 0.68 g (1.65 mmol) of the compound obtained in the preceding Step 2 in 45 ml of anhydrous DMF are added successively 18 mg $\text{Pd}(\text{OAc})_2$, 8 mg of CuI, 330 mg of K_2CO_3 , and 0.22 ml of ethyl acrylate. After 30 minutes under reflux, the reaction mixture is concentrated under vacuum. The residue is taken up in dichloromethane. The organic phase is filtered, washed two times with water, dried over Na_2SO_4 and then concentrated under vacuum. The crude product is purified by chromatography over silica gel (dichloromethane/methanol 97/3) and then crystallized from ether to give 0.320 g (yield 57%) of the desired compound.

25 TLC CH_2Cl_2 / MeOH 97.5/2.5 $R_f = 0.50$

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NMR. CDCl_3 ^1H δ (ppm) 1.40 (t,3H), 3.70 (s,3H), 4.40 (q,2H), 5.30 (s,2H), 7.2-7.30 (m,3H), 7.5-7.55 (m,2H), 9.0 (s,1H), 9.2 (s,1H)

**Step 4 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine
-6-carboxylic acid**

5 The compound is obtained by hydrolysis, in a mixture of dioxan/water in presence of LiOH, of the compound obtained in the preceding Step 3

TLC CH_2Cl_2 / MeOH 90 / 10 R_f = 0.10

NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 5.20 (s,2H), 7.2-7.40 (m,5H), 8.75 (s,1H), 9.2 (s,1H), 13.5 (bs,1H)

10 HPLC = 100%

**Step 5 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine
-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 4 and piperonylamine.

15 TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.60

NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 4.40 (d,2H), 5.2 (s,2H), 5.95 (s,2H), 6.75-6.95 (m,3H), 7.2-7.40 (m,5H), 8.85 (s,1H), 9.2 (s,1H), 9.25 (t,1H)

IR 3271, 1709, 1665, 1630, 1614, 1488, 1248, 1042, 937, 795 cm^{-1}

MP = 174 $^{\circ}\text{C}$

20 HPLC 97.5 %

**Example 164 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-
2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid**

**Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-
carboxylic acid**

25 A solution of 1.3 g (4.17 mmol) of the compound obtained in the Step 4 of Example 163 and 3.1 g (23 mmol) of AlCl_3 in 44 ml of benzene is stirred 2 hours at room temperature. After addition of a mixture water/ice, the reaction mixture is extracted successively with

ethyl acetate and dichloromethane. The aqueous layer is acidified at pH 1 by addition of concentrated HCl. The precipitate obtained is filtered off and washed with 10 ml of methanol and 10 ml of dichloromethane to provide the desired compound (yield 62.9%)

NMR (DMSO) ^1H δ (ppm): 3.50 (s, 3H), 8.60 (s, 1H), 9.10 (s, 1H), 11.9 (bs, 1H), 13.5 (bs, 1H)

HPLC = 100%

Step 2 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 2 and 4-methoxybenzylamine.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.45

NMR (DMSO) ^1H δ (ppm): 3.50 (s, 3H), 3.7 (s, 3H), 4.40 (d, 2H), 6.85-6.95 (m, 2H), 7.25-7.30 (m, 2H), 8.80 (s, 1H), 9.15 (s, 1H), 9.30 (t, 1H), 11.85 (bs, 1H)

HPLC = 92%

Step 3 Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoate

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate. After concretization in ether 0.41 g (yield 71.1%) of the desired compound is isolated.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.80

NMR (DMSO) ^1H δ (ppm): 3.60 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 4.45 (d, 2H), 5.2 (s, 2H), 6.90 (dd, 2H), 7.30 (dd, 2H), 7.50 (dd, 2H), 7.90 (dd, 2H), 8.90 (s, 1H), 9.20 (s, 1H), 9.30 (t, 1H),

HPLC = 96.8%

Step 4 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of Example 35 using the compound obtained in the preceding Step 3

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NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 4.45 (d,2H), 5.20 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.45 (d,2H), 7.90 (d,2H), 8.85 (s,1H), 9.20 (s,1H), 9.30 (t,1H), 12.90 (bs,1H)

IR 3292, 1718, 1695, 1667, 1633, 1609, 1497, 1301, 1242, 797 cm^{-1}

5 M.P = 229.5 $^{\circ}\text{C}$

HPLC 93.6 %

**Example 165 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido
[2,3-d] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

10 The compound is obtained (0.11 g, yield=68.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-(bromomethyl)benzonitrile.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.70

NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.90 (d,2H), 7.30 (d,2H), 7.55 (d,2H), 7.80 (d,2H), 8.85 (s,1H), 9.20 (s,1H), 9.30 (t,1H)

15 IR 3230, 2230, 1710, 1673, 1635, 1609, 1494, 1303, 1252, 794 cm^{-1}

M.P = 197 $^{\circ}\text{C}$

HPLC 97.2 %

**Example 166 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido
[2,3-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

20 The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in Step 2 of Example 164 and 4-fluorobenzyl bromide.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.70

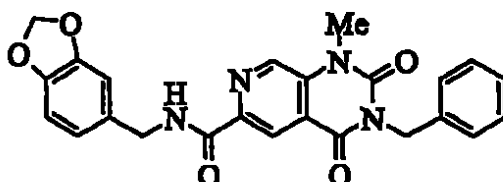
25 NMR. DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 4.40 (d,2H), 5.10 (s,2H), 6.8-6.90 (m,2H), 7.1-7.2 (m,2H), 7.25-7.35 (m,2H), 7.4-7.50 (m,2H), 8.85 (s,1H), 9.15 (s,1H), 9.30 (t,1H)

IR 3260, 1709, 1664, 1616, 1497, 1245, 1221, 1035, 796 cm^{-1}

M.P = 211.5 $^{\circ}\text{C}$

HPLC 98.3 %

**Example 167 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide**



Step 1 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde

5 A solution of 9.5 g (43.9 mmol) of 3-benzyl-6-methyl-1H-pyrimidine-2,4-dione (*Synthetic Communications* 1991, 2181-2188) and 129 ml of cold acetic acid are stirred 5 minutes, and 5.75 g of SeO₂ are added. The reaction mixture is heated to reflux for 2h30, filtered and concentrated under vacuum. The residue is taken up in dichloromethane. The
10 insoluble part is eliminated and the filtrate is concentrated under vacuum. A chromatography over silica gel (dichloromethane/methanol 95/5) provides 4.0 g of the desired compound (yield 39.5%).

NMR. CDCl₃ ¹H δ (ppm) 5.20 (s, 2H), 6.30 (s, 1H), 7.2-7.30 (m, 3H), 7.40-7.50 (m, 2H), 9.0 (bs, 1H), 9.60 (s, 1H)

**Step 2 1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidine-4-carbaldehyde
dimethylhydrazone**

15 To a stirred solution of 3.6 g (15.6 mmol) of the compound obtained in the preceding Step 1 in 80 ml of anhydrous DMF are added 1.2 ml (0.94 g, 15.6 mmol) of dimethylhydrazine. After 1 hour of stirring at room temperature, the solvent is removed under vacuum and the residue is taken up in dichloromethane. The organic layer is washed, dried over Na₂SO₄
20 and concentrated. A chromatography over silica gel (dichloromethane/methanol 97/3) provides 2.5 g (yield 59%) of the desired compound.

NMR. CDCl₃ ¹H δ (ppm) 3.10 (s, 6H), 5.10 (s, 2H), 5.55 (s, 1H), 6.50 (s, 1H), 7.2-7.30 (m, 3H), 7.40-7.50 (m, 2H), 8.50 (bs, 1H)

**Step 3 1-Benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-
carbaldehyde dimethylhydrazone**

25

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To a stirred solution of 2.3 g (8.45 mmol) of the compound obtained in the preceding Step 2 in 58 ml of anhydrous DMF are added 2.3 ml (2.0 g, 1.69 mmol) of *N,N*-dimethylformamide acetal. The reaction mixture is maintained at 100°C for 10 minutes and concentrated under vacuum. The residue is taken up in dichloromethane and the product is precipitated by addition of ether to provide 1.75 g (yield 72.3%) of the desired compound.

5 NMR. CDCl₃, ¹H δ (ppm): 3.20 (s, 6H), 3.50 (s, 3H), 5.15 (s, 2H), 6.10 (s, 1H), 6.60 (s, 1H), 7.2-7.30 (m, 3H), 7.40-7.50 (m, 2H).

Step 4 Methyl 1-benzyl-2,6-dioxo-3-methyl-1,2,3,6-tetrahydro-pyrimidine-4-(carbaldehyde dimethylhydrazone)-5-carboxylate

10 To a stirred solution of 1.7 g (5.94 mmol) of the compound obtained in the preceding Step 3 in 61 ml of anhydrous acetonitrile are added successively 1.68 g (7.1 mmol) of Pd(OAc)₂ and 0.613 g (7.1 mmol) of methyl acrylate. After 20 minutes of stirring under reflux the reaction mixture is filtered off and concentrated under vacuum. The residue is chromatographed over silica gel (dichloromethane/methanol 97/3) to provide 1.40 g

15 (yield 63.6%) of the desired compound.

NMR. CDCl₃, ¹H δ (ppm): 3.20 (s, 6H), 3.55 (s, 3H), 3.75 (s, 3H), 5.20 (s, 2H), 6.70 (s, 1H), 7.1-7.70 (m, 7H).

Step 5 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid methyl ester

20 A solution of 1.4 g (3.78 mmol) of the compound obtained in the preceding Step 4, 18 ml of chlorobenzene and 3.6 ml of acetic acid is stirred under reflux for 3 hours, and concentrated under vacuum to provide 1.4 g of a precipitate. The desired compound (0.76 g, yield 62%) is obtained by recrystallization of the crude product in 120 ml of ethyl acetate.

25 NMR. CDCl₃, ¹H δ (ppm): 3.70 (s, 3H), 4.0 (s, 3H), 5.30 (s, 2H), 7.2-7.35 (m, 3H), 7.45-7.55 (m, 2H), 8.80 (s, 1H), 8.85 (s, 1H).

Step 6 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid

- 0.76 g (2.34 mmol) of the compound obtained in the preceding Step 5, 7.6 ml of methanol, 7.6 ml of water and 0.646 g (4.67 mmol) of K_2CO_3 are stirred overnight at room temperature and then heated to reflux for 5 minutes. After cooling and addition of water the acidification to pH 1 of the mixture provides a precipitate which is dissolved in a mixture of methanol/dichloromethane. The organic layer is washed with water, dried and concentrated under vacuum. The residue obtained is concretized in a mixture of dichloromethane/ether to give 0.54 g (yield 74%) of the desired compound.
- NMR.DMSO ^1H δ (ppm) 3.60 (s,3H), 5.20 (s,2H), 7.2-7.40 (m,5H), 8.50 (s,1H); 9.0 (s,1H), 13.3 (bs,1H)
- M.P = 240°C
- HPLC = 100%

Step 7 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

- The compound is obtained according to the procedure of the Example 1 using the compound obtained in the preceding Step 6 and piperonylamine.
- TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.60
- NMR.DMSO ^1H δ (ppm) 3.65 (s,3H), 4.40 (d,2H), 5.15 (s,2H), 5.95 (s,2H), 6.75-6.85 (m,2H), 6.90 (s,1H), 7.2-7.40 (m,5H), 8.45 (s,1H), 8.90 (s,1H), 9.25 (t,1H)
- IR 3387, 1716, 1662, 14875, 1442, 1250, 1239, 1040, 789 cm^{-1}
- M.P = 197.5 °C
- HPLC : 100 %

Example 168 Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate

- Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid**
- 3.3 g (10.6 mmol) of the compound obtained in the Step 6 of Example 167 are treated according to the procedure described in the Step 1 of Example 164 to give 2.0 g (yield 85.3%) of the desired compound.

NMR.DMSO ^1H δ (ppm) 3.60 (s,3H), 8.40 (s,1H), 8.95 (s,1H), 12.0 (s,1H), 12.90 (bs,1H)

HPLC = 100%

5 **Step 2 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained (yield 78%) according to the procedure of the Example 1 using the compound obtained in the preceding Step 1 and 4-methoxybenzylamine.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.50

10 NMR.DMSO ^1H δ (ppm) 3.60 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 6.85 (dd,2H), 7.25 (dd,2H), 8.40 (s,1H), 8.85 (s,1H), 9.20 (t,1H), 12.0 (s,1H)

HPLC = 99 %

Step 3 Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate

15 The compound is obtained (0.2 g, yield 77%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 2 and methyl-4-(bromomethyl)benzoate.

TLC CH_2Cl_2 / MeOH 95/5 R_f = 0.80

20 NMR.DMSO ^1H δ (ppm) 3.60 (s,3H), 3.70 (s,3H), 3.85 (s,3H), 4.50 (d,2H), 5.20 (s,2H), 6.85 (d,2H), 7.20 (d,2H), 7.50 (d,2H), 7.90 (d,2H), 8.5 (s,1H), 8.90 (s,1H), 9.20 (t,1H)

IR 3396, 1719, 1661, 1439, 1279, 1250, 1110, 753 cm^{-1}

M.P = 211.1 °C

HPLC 99.5 %

25 **Example 169 tert-Butyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate**

The compound is obtained (yield 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of example 168 and *tert*-butyl 4-bromomethyl-benzoate.

TLC CH₂Cl₂ / MeOH 95/5 R_f = 0.80

5 NMR.DMSO ¹H δ (ppm) 1.50 (s,9H), 3.65 (s,3H), 3.75 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.85 (dd,2H), 7.25 (dd,2H), 7.45 (dd,2H), 7.85 (dd,2H), 8.50 (s,1H), 8.90 (s,1H), 9.2 (t,1H),
HPLC = 98 %

10 **Example 170 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid**

Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 3-methoxy-benzylamide

The compound is obtained (yield 62.4%) according to the procedure of the Example 1 using the compound obtained in the Step 1 of Example 168 and 3-methoxybenzylamine.

15 TLC CH₂Cl₂ / MeOH 95/5 R_f = 0.50

NMR.DMSO ¹H δ (ppm) 3.60 (s,3H), 3.75 (s,3H), 4.50 (d,2H), 6.75-6.95 (m,3H), 7.20-7.30 (m,1H), 8.40 (s,1H), 8.85 (s,1H), 9.25 (t,1H), 12.0 (s,1H)
HPLC = 98 %

20 **Step 2: *tert*-Butyl 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate**

The compound is obtained (yield 80.4%) according to the procedure of the Step 2 of Example 34 using the compound obtained in the preceding Step 1 and *tert*-butyl 4-(bromomethyl)benzoate

TLC CH₂Cl₂ / MeOH 95/5 R_f = 0.80

25 NMR.DMSO ¹H δ (ppm) 1.50 (s,9H), 3.65 (s,3H), 3.75 (s,3H), 4.50 (d,2H), 5.20 (s,2H), 6.80-6.95 (m,3H), 7.20-7.30 (m,1H), 7.5 (dd,2H), 7.85 (dd,2H), 8.50 (s,1H), 8.95 (s,1H), 9.3 (t,1H),
HPLC = 93.6 %

Step 3 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid

The compound is obtained according to the procedure of the Step 2 of Example 169 using the compound obtained in the preceding Step 2

5 **TLC** CH₂Cl₂ / MeOH 95/5 R_f = 0.60

NMR DMSO ¹H δ (ppm) 3.65 (s,3H), 3.75 (s,3H), 4.50 (d,2H), 5.20 (s,2H), 6.75-6.80 (s,1H), 6.90 (s,2H), 7.20-7.25 (m,1H), 7.45 (d,2H), 7.85 (d,2H), 8.5 (s,1H), 8.90 (s,1H), 9.30 (t,1H), 12.95 (bs,1H)

IR 3378, 1712, 1660, 1600, 1439, 1266, 1056, 790 cm⁻¹

10 **M.P.** = 208.1 °C

HPLC 96.6 %

Example 171 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained according to the procedure of the Step 2 of Example 34 using the compound obtained in the Step 2 of Example 168 and (4-bromomethyl)-benzomitrile

15 **TLC** CH₂Cl₂ / MeOH 95/5 R_f = 0.80

NMR DMSO ¹H δ (ppm) 3.65 (s,3H), 3.75 (s,3H), 4.45 (d,2H), 5.25 (s,2H), 6.90 (d,2H), 7.25 (d,2H), 7.55 (d,2H), 7.80 (d,2H), 8.5 (s,1H), 8.95 (s,1H), 9.20 (t,1H)

IR 3391, 2228, 1716, 1662, 1443, 1331, 1251, 789 cm⁻¹

20 **M.P.** = 230 °C

HPLC 98.8 %

Example 172 3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1H-quinazoline-2,4-dione

The compound of the preparation C is treated by SOCl₂ in THF to give its chloride derivate which is reacted with phenetyl magnesium bromide and CuI in presence of THF. After usual treatment the desired compound is obtained.

25

NMR. CDCl_3 ^1H δ (ppm) 3.0 (m, 2H), 3.30 (m, 2H), 3.60 (s, 3H), 5.25 (s, 2H), 7.10-7.35 (m, 9H), 7.50 (m, 2H), 8.3 (m, 1H), 8.80 (s, 1H)

M.P. = 155 °C

HPLC 98.0 %

5 **Example 173 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester**

NMR CDCl_3 ^1H δ (ppm) 3.60 (s, 3H), 5.0 (d, 2H), 5.30 (s, 2H), 6.5-6.7 (m, 2H), 7.15-7.35 (m, 6H), 7.55 (m, 2H), 8.40 (m, 1H), 8.60 (m, 2H), 9.0 (s, 1H)

M.P. = 147 °C

10 HPLC 97.5 %

Example 174 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester

NMR CDCl_3 ^1H δ (ppm) 3.60 (s, 3H), 5.0 (d, 2H), 5.30 (s, 2H), 6.5 (m, 1H), 6.8 (d, 1H), 7.30 (m, 5H), 7.60 (m, 2H), 7.7 (d, 1H), 8.40 (d, 1H), 8.55 (m, 1H), 8.70 (s, 1H), 9.0 (s, 1H)

15 M.P. = 184 °C

HPLC 99.6 %

Example 175 3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1H-quinazoline-2,4-dione

TLC CH_2Cl_2 / MeOH 98/2 R_f = 0.20

20 NMR CDCl_3 ^1H δ (ppm) 3.65 (s, 3H), 4.45 (s, 2H), 5.25 (s, 2H), 7.18 (d, 2H), 7.20-7.35 (m, 4H), 7.50 (d, 2H), 8.3 (d, 1H), 8.40 (d, 2H), 8.80 (s, 1H)

IR 1706, 1693, 1657, 1610, 1574, 1508, 1480, 1448, 1428, 1321, 1307, 1206, 1093, 831, 810, 782, 703 cm^{-1}

M.P. = 187 °C

25 HPLC 98.0 %

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Example 176 3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

The compound is obtained by catalytic hydrogenation of the compound of Example 60 using Raney Ni and NH₃ in methanol

5 TLC CH₂Cl₂ / MeOH / NH₄OH 90/10 / 1 R_f = 0.25

NMR. CDCl₃ ¹H δ (ppm) 1.45-1.70 (m, 2H), 3.6 (s, 3H), 3.8 (m, 5H), 4.55 (d, 2H), 5.22 (s, 2H), 6.74 (m, 1H), 6.86 (d, 2H), 7.2-7.30 (m, 5H), 7.44 (d, 2H), 8.28 (d, 1H), 8.48 (s, 1H)

10 IR 3370, 1702, 1655, 1640, 1617, 1542, 1508, 1477, 1324, 1303, 1247, 1173, 1032, 829, 786, 756 cm⁻¹

M.P. = 187 °C

HPLC 98.4%

Example 177 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

15 The compound is obtained according to the procedure of the Step 2 of Example 34 using 2-(4-bromomethylphenyl)-benzonitrile.

TLC CH₂Cl₂ / MeOH 98.5/1.5 R_f = 0.20

20 NMR. CDCl₃ ¹H δ (ppm) 3.65 (s, 3H), 3.80 (s, 3H), 4.55 (d, 2H), 5.30 (s, 2H), 6.55-6.65 (m, 1H), 6.25 (d, 2H), 7.2-7.30 (m, 3H), 7.35-7.50 (m, 4H), 7.55-7.65 (m, 3H), 7.75 (d, 1H), 8.25-8.35 (m, 1H), 8.45 (s, 1H)

IR 1702, 1661, 1629, 1508, 1478, 1332, 1242, 1036, 833, 766 cm⁻¹

M.P. = 200 °C

HPLC 99.8%

25 **Example 178 1-Methyl-2,4-dioxo-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide**

The compound is obtained according to the procedure of the Step 2 of Example 34 using 5-[(4-bromomethyl)biphenyl]-tetrazole

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.50

5 NMR DMSO ¹H δ (ppm) 3.55 (s, 3H), 3.75 (s, 3H), 4.40 (d, 2H), 5.15 (s, 2H), 6.90 (d, 2H), 7.05 (d, 2H), 7.25 (d, 4H), 7.45-7.70 (m, 6H), 8.30 (d, 1H), 8.6 (s, 1H), 9.25 (m, 1H)

IR 2943, 1702, 1656, 1618, 1510, 1477, 1450, 1323, 1302, 1247, 1032, 829, 814, 782, 757 cm⁻¹

HPLC 99.6 %

10 **Example 179. Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate**

The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethylphenyl)benzoate

TLC CH₂Cl₂ / MeOH 97/3 R_f = 0.30

15 NMR DMSO ¹H δ (ppm) 3.61 (s, 3H), 3.62 (s, 3H), 3.80 (s, 3H), 4.55 (d, 2H), 5.30 (s, 2H), 6.65 (t, 1H), 6.85 (d, 2H), 7.2-7.30 (m, 6H), 7.35-7.40 (m, 1H), 7.45-7.55 (m, 3H), 7.80 (d, 1H), 8.27 (d, 1H), 8.47 (s, 1H)

IR 1707, 1668, 1656, 1638, 1616, 1509, 1478, 1330, 1294, 1248, 1089, 765, 754 cm⁻¹

M.P = 172 °C

20 HPLC 99.7 %

Example 180 4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid

The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 179

25 TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.40

NMR DMSO ^1H δ (ppm) 3.57 (s,3H), 3.72 (s,3H), 4.42 (d,2H), 5.20 (s,2H), 6.90 (d,2H), 7.25-7.45 (m,8H), 7.50-7.60 (m,2H), 7.70 (d,1H), 8.26 (d,1H), 8.60 (s,1H), 9.17-9.27 (m,1H), 12.5-13.2 (m,1H)

IR 1698, 1668, 1655, 1639, 1612, 1508, 1479, 1330, 1304, 1248, 765, 754 cm^{-1}

5 M.P. = 175 °C

HPLC 100 %

Example 181 Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate

10 The compound is obtained according to the procedure of the Step 2 of Example 34 using Methyl 4-(bromomethyl)-2-fluoro-benzoate.

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.60

NMR. CDCl_3 ^1H δ (ppm) 1.30 (t,3H), 3.60 (s,3H), 3.80 (s,3H), 4.35 (q,2H), 4.60 (m,2H), 5.30 (s,2H), 6.55 (m,1H), 6.90 (m,2H), 7.30 (m,5H), 7.90 (m,1H), 8.30 (m,1H), 8.50 (s,1H),

15 M.P. = 156 °C

HPLC 100 %

Example 182 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid

20 The compound is obtained according to the procedure of the Step 2-4 of Preparation B using the compound of Example 181

TLC CH_2Cl_2 / MeOH 90/10 R_f = 0.20

NMR DMSO ^1H δ (ppm) 3.60 (s,3H), 3.75 (s,3H), 4.40 (m,2H), 5.20 (s,2H), 6.90 (m,2H), 7.30 (m,4H), 7.60 (d,1H), 7.80 (m,1H), 8.30 (m,1H), 8.70 (s,1H), 9.2 (s,1H), 13.2 (s,1H)

25 M.P. = 160 °C

HPLC 100 %

Example 183 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylaminoethyl ester

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.20

5 NMR CDCl₃ ¹H δ (ppm) 2.3 (s,6H), 2.60 (m,2H), 3.60 (s, 3H), 3.75 (s,3H), 3.85 (s,3H), 4.35 (m,2H), 4.55 (m,2H), 5.25 (s,2H), 6.50 (m,1H), 6.80 (m,2H), 7.10 (d,1H), 7.25 (m,4H), 7.70 (d,1H), 8.25 (m,1H), 8.5 (s,1H)

M.P. = 130 °C

HPLC 97.3 %

10 **Example 184** 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylaminoethyl ester

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.60

15 NMR CDCl₃ ¹H δ (ppm) 2.3 (s,6H), 2.55 (s,3H), 2.70 (m,2H), 3.60 (s, 3H), 3.80 (s,3H), 4.40 (m,2H), 4.60 (m,2H), 5.20 (s,2H), 6.60 (s,1H), 6.80 (m,2H), 7.30 (m,5H), 7.80 (m,1H), 8.30 (m,1H), 8.5 (s,1H)

M.P. = 146 °C

HPLC 99 %

20 **Example 185** 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxybenzylamide

TLC CH₂Cl₂ / MeOH 90/10 R_f = 0.30

25 NMR.DMSO ¹H δ (ppm) 3.2 (m,1H), 3.55 (s, 3H), 3.70 (s,3H), 4.40 (d,2H), 5.20 (s,2H), 6.90 (m,2H), 7.25 (m,2H), 7.40 (m,2H), 7.55 (m,1H), 7.70 (m,2H), 8.30 (m,1H), 8.60 (s,1H), 9.2 (m,1H)

M.P. = 305 °C

HPLC 100 %

Example 186 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-phenyl]-acetic acid

5 **TLC** CH₂Cl₂ / MeOH 90/10 R_f = 0.35

NMR. DMSO ¹H δ (ppm) 3.50 (m, 5H), 3.70 (s, 3H), 4.40 (d, 2H), 6.80 (d, 2H), 7.20 (m, 4H), 7.40 (d, 2H), 7.60 (d, 1H), 8.30 (d, 1H), 8.60 (s, 1H), 9.2 (t, 1H)

IR = 1717, 1645, 1619, 1501, 1298, 1240, 823, 750

HPLC 100 %

10 **Example 187** 1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide

TLC CH₂Cl₂ / MeOH 95/5 R_f = 0.58

NMR. DMSO ¹H δ (ppm) 2.0 (d, 3H), 3.45 (s, 3H), 4.40 (d, 2H), 6.00 (s, 2H), 6.80-6.95 (m, 4H); 7.4-7.50 (m, 3H), 7.55 (t, 1H), 7.85-8.0 (m, 4H), 8.20 (d, 1H), 8.6 (s, 1H), 9.15 (t, 1H)

15

IR 1656, 1618, 1503, 1440, 1254, 1040, 777, 754 cm⁻¹

M.P = 157 °C

HPLC 96.2 %

20 **Example 188** 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid

To a stirred solution of 0.5 g (0.9 mmol) of the compound obtained in the Example 169 in 50 ml of dichloromethane are added 5 ml of trifluoroacetic acid. The mixture is stirred overnight at room temperature and 60 ml of ether are added. The product crystallizes and after filtration 0.44 g (yield 100%) of the desired compound is obtained.

25 **TLC** CH₂Cl₂ / MeOH 95/5 R_f = 0.60

NMR. DMSO ^1H δ (ppm) 3.65 (s, 3H), 3.75 (s, 3H), 4.45 (d, 2H), 5.25 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.50 (d, 2H), 7.90 (d, 2H), 8.5 (s, 1H), 8.95 (s, 1H), 9.20 (t, 1H), 12.85 (bs, 1H)

IR 3388, 1715, 1662, 1475, 1442, 1247, 791 cm^{-1}

M.P = 264.4 $^{\circ}\text{C}$

5 HPLC 98.9 %

Example 189 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

10 To 0.5 g (1.5 mmol) of the compound of Preparation D in dimethylformamide (10 ml) are added EDAC.HCl 0.38g (1.9 mmol), HOBT 0.27 g (1.9 mmol), followed by 4-pyridyl-benzylamine 0.21 g (1.9 mmol). The mixture is stirred 48 hours at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO_4 , recrystallized solid product in hot ethyl acetate to obtain 0.13 g (yield 20%) of the desired compound.

15 MS m/z (APCI, AP+) 419.2 $[\text{M}]^+$

CHN Analysis Calcd (%) C, 66.02, H, 4.58, N, 13.39

Found (%) C, 65.73, H, 4.47, N, 13.36

20 **Example 190 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide**

0.10 g (yield 17%) of the desired compound is obtained according to the procedure of Example 189, but using 2-methoxy-4-pyridyl-benzylamine.

MS m/z (APCI, AP+) 449.2 $[\text{M}]^+$

25 CHN Analysis $\text{C}_{24}\text{H}_{21}\text{FN}_4\text{O}_4 \cdot 0.1 \text{H}_2\text{O}$

Calcd (%) C, 64.02, H, 4.75, N, 12.44

Found (%) C, 63.66, H, 5.07, N, 12.16

Example 191 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.11 g (yield 26%) of the desired compound is obtained according to the procedure of Example 189, but using 3-pyridyl-benzylamine.

MS m/z (APCI, AP+) 419.1 $[M]^+$

CHN Analysis $C_{23}H_{19}FN_4O_3 \cdot 1.2 H_2O$

5 Calcd (%) C, 62.78, H, 4.90, N, 12.73

Found (%) C, 62.75, H, 4.90, N, 12.73

Example 192 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

10 0.12 g (yield 35%) of the desired compound is obtained according to the procedure of Example 189, but using 4-methoxy-benzylamine.

MS m/z (APCI, AP+) 448.1 $[M]^+$

CHN Analysis $C_{25}H_{22}FN_3O_4 \cdot 0.1 H_2O$

Calcd (%) C, 66.84, H, 4.98, N, 9.35

Found (%) C, 66.57, H, 4.83, N, 9.03

15 **Example 193 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide**

0.20 g (yield 59%) of the desired compound is obtained according to the procedure of Example 189, but using 3-methoxy-benzylamine.

MS m/z (APCI, AP+) 448.1 $[M]^+$

20 CHN Analysis $C_{25}H_{22}FN_3O_4$

Calcd (%) C, 67.11, H, 4.96, N, 9.39

Found (%) C, 66.82, H, 4.87, N, 9.11

Example 194 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

0.13 g (yield 20%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of the Preparation E and 4-pyridyl-benzylamine.

MS m/z (APCI, AP+) 433.2 $[M]^+$

CHN Analysis. Calcd (%) C, 66.66, H, 4.89, N, 12.96

5 Found (%) C, 66.26, H, 4.71, N, 12.78

Example 195 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.18 g (yield 51%) of the desired compound is obtained according to the procedure of Example 189, but using the compound of Preparation E and 3-pyridyl-benzylamine.

10 MS m/z (APCI, AP+) 433.1 $[M]^+$

CHN Analysis Calcd (%) C, 66.66, H, 4.89, N, 12.96

Found (%) C, 66.43, H, 5.03, N, 12.84

Example 196 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

15 **Step 1 Methyl 3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

4.6 g (yield 59%) of the desired compound is obtained according to the procedure of Step 1 of Preparation D, but using 4-bromobenzyl isocyanate

MS m/z (APCI, AP+) 388.9 $[M]^+$

20 CHN Analysis Calcd (%) C, 52.46, H, 3.37, N, 7.20

Found (%) C, 52.16, H, 3.30, N, 7.30

Step 2 Methyl 1-methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

1.49 g (yield 71%) of the desired compound is obtained according to the procedure of step 2 of Preparation D, but using the compound obtained in the Preceding Step 1

25 MS m/z (APCI, AP+) 404.9 $[M]^+$

CHN Analysis Calcd (%) C, 53.62, H, 3.75, N, 6.95

674

167

Found (%) C, 53.24, H, 3.71, N, 6.84

Step 3 1-Methyl-3-(4-bromobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.3 g (yield 87%) of the desired compound is obtained according to the procedure of Step 2-4 of Preparation B, but using the compound obtained in the preceding Step 2

MS m/z (APCI, AP+) 388.9 $[M]^+$

CHN Analysis Calcd (%) C, 52.46, H, 3.37, N, 7.20

Found (%) C, 52.12, H, 3.30, N, 7.11

Step 4 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

10

0.24 g (yield 76%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-methoxy-benzylamine.

MS m/z (APCI, AP+) 508 $[M]^+$

15

CHN Analysis $C_{23}H_{22}BrN_3O_4 \cdot 0.2 H_2O$

Calcd (%) C, 58.65, H, 4.41, N, 8.21

Found (%) C, 58.32, H, 4.32, N, 8.12

Example 197 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

20

0.22 g (yield 33%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 2-methoxy-4-pyridyl-benzylamine.

NMR. DMSO ^1H δ (ppm) 3.52 (3H,s), 3.79 (3H,s), 4.43 (2H,d), 5.09 (2H,s), 6.66 (1H,s), 6.89 (1H,d), 7.26-7.56 (5H,m), 8.06 (1H,d), 8.24-8.26 (1H,m), 8.61 (1H,m), 9.31 (1H,t)

25

MS m/z (APCI, AP+) 509 $[M]^+$

Example 198 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

Step 1 Methyl 3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

The compound is obtained with 51% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3,4-difluorobenzylamine.

NMR DMSO ^1H (ppm) 3.86 (3H,s), 5.05 (2H,s), 6.66 (1H,s), 7.18-7.43 (4H,m), 8.18 (1H,dd), 8.47 (1H,s)

MS m/z (APCI, AP+) 347.1 $[\text{M}]^+$

Step 2 Methyl 1-methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate

1.5 g (yield 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1

MS m/z (APCI, AP+) 361.0 $[\text{M}]^+$

CHN Analysis Calcd (%) C, 60.00, H, 3.92, N, 7.77

Found (%) C, 60.05, H, 3.85, N, 7.72

Step 3 1-Methyl-3-(3,4-difluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

1.1 g (yield 82%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2

MS m/z (APCI, AP+) 437.0 $[\text{M}]^+$

CHN Analysis Calcd (%) C, 58.96, H, 3.49, N, 8.09

Found (%) C, 58.67, H, 3.99, N, 7.27

Step 4 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.48 g (yield 79%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 3-pyridylbenzylamine.

MS m/z (APCI, AP+) 437.1 $[\text{M}]^+$

675

CHN Analysis $C_{23}H_{18}F_2N_4O_3 \cdot 0.2 H_2O$

Calcd (%) C, 62.78, H, 4.21, N, 12.73

Found (%) C, 62.50, H, 4.13, N, 12.82

5 **Example 199 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide**

0.23 g (yield 38%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-pyridyl-benzylamine.

MS m/z (APCI, AP+) 437.1 $[M]^+$

10 CHN Analysis $C_{23}H_{18}F_2N_4O_3$

Calcd (%) C, 63.30, H, 4.16, N, 12.84

Found (%) C, 63.19, H, 4.07, N, 12.81

Example 200 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

15 0.11 g (yield 39%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 198 and 4-methoxy-benzylamine.

MS m/z (APCI, AP+) 466.2 $[M]^+$

CHN Analysis $C_{25}H_{21}F_2N_3O_4$

20 Calcd (%) C, 64.51, H, 4.55, N, 9.03

Found (%) C, 64.41, H, 4.53, N, 8.87

Example 201 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

25 **Step 1 Methyl 3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

The compound is obtained with 18.1% yield according to the procedure of Step 1-5 to Step 2-5 of Preparation B using as substrates the compound of Preparation A and 3-chloro-4-fluorobenzylamine.

MS m/z (APCI, AP⁺) 361.0 [M]⁺

5 **Step 2 Methyl 1-methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**

0.5 g (yield 72%) of the desired compound is obtained according to the procedure of Step 2 of the Preparation D, but using the compound obtained in the preceding Step 1

MS m/z (APCI, AP⁺) 377.0 [M]⁺

10 **CHN Analysis** Calcd (%) C, 57.38, H, 3.75, N, 7.44
 Found (%) C, 57.34, H, 3.73, N, 7.27

Step 3 1-Methyl-3-(3-chloro-4-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

0.45 g (yield 92%) of the desired compound is obtained according to the procedure of Step 2-4 of the Preparation B, but using the compound obtained in the preceding Step 2

MS m/z (APCI, AP⁺) 363.0 [M]⁺

15 **CHN Analysis** Calcd (%) C, 56.29, H, 3.33, N, 7.72
 Found (%) C, 56.24, H, 3.21, N, 7.64

Step 4 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

20 0.17 g (yield 69%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the preceding Step 3 and 4-pyridylbenzylamine.

MS m/z (APCI, AP⁺) 453.1 [M]⁺

25 **CHN Analysis** C₂₃H₁₈F₂N₄O₃ · 1.1 H₂O
 Calcd (%) C, 58.44, H, 4.31, N, 11.85
 Found (%) C, 58.23, H, 4.23, N, 11.75

676

Example 202 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide

0.21 g (yield 80%) of the desired compound is obtained according to the procedure of Example 189, but using the compound obtained in the Step 3 of the Example 201 and 4-methoxy-benzylamine

MS m/z (APCI, AP+) 482.1 $[M]^+$

CHN Analysis $C_{25}H_{21}ClFN_3O_4$

Calcd (%) C, 62.31, H, 4.39, N, 8.72

Found (%) C, 62.12, H, 4.37, N, 8.51

Example 203 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in hot methanol is added 0.22 g (1.03 mmol) choline bicarbonate. The mixture is heated to reflux for 1 hour. Cool and concentrate. The resulting solid is recrystallized from ethanol to provide 0.41 g (yield 68%) of the desired compound.

CHN Analysis $C_{31}H_{36}N_4O_7 \cdot 0.5 H_2O$

Calcd (%) C, 63.58, H, 6.37, N, 9.57

Found (%) C, 63.32, H, 6.58, N, 9.57

Example 204 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium salt

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and $CaCl_2$ 0.058 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 0.49 g (yield 94%) of the desired compound.

CHN Analysis: $C_{22}H_{24}CaN_4O_{12} \cdot 1.0 H_2O$

Calcd (%) C, 62.27, H, 4.62, N, 8.38

Found (%) C, 61.95, H, 4.70, N, 8.34

Example 205 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium salt

A suspension of 0.5 g (1.05 mmol) of compound of the Example 34 in warm tetrahydrofuran is added 1.05 ml 1.00 N NaOH. The mixture is stirred 0.5 hour and $MgCl_2$ 0.052 g (0.525 mmol) is added in one portion. The mixture is stirred 2 hours and then concentrated. Add ethanol and filter. Dried at 88°C in vacuum oven for 72 hours gives 0.49 g (yield 96%) of the desired compound.

CHN Analysis $C_{22}H_{24}MgN_6O_{12} \cdot 1.0 H_2O$

Calcd (%) C, 63.26, H, 4.70, N, 8.51

Found (%) C, 63.07, H, 4.89, N, 8.50

Example 206 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridazin-4-ylmethyl)-amide

To a suspension of compound of the Step 1 of the Example 33 (1.00 g, 4.54 mmol), EDAC (1.13 g, 5.90 mmol), HOBT (0.675 g, 5.00 mmol) in 20 ml of DMF is added a solution of 4-aminomethyl-pyridine (0.507 ml, 5.00 mmol). The light orange suspension is stirred at room temperature overnight. After 24 h, the reaction mixture is concentrated affording a offwhite solid. The solids are subsequently washed with 10 ml of ethyl acetate, saturated Na_2CO_3 , and 10 ml of H_2O to give 1.20 g (yield 85.7%) of product.

MP 141-145 °C

MS(APCI+) m/z 309.1 (MH)

Step 2 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

To a suspension of compound obtained in the preceding Step 1 (0.200 g, 0.645 mmol) in 6 ml of DMF is added Cs_2CO_3 (0.630 g, 1.93 mmol). After stirring at room temperature for 30 min, a solution of 4-chlorobenzyl-bromide (0.132 g, 0.645 mmol) in 2 ml of DMF is added dropwise to the reaction mixture and stirred overnight. White solids (cesium salt) are
5 filtered and the solution was concentrated. The resulting suspension is diluted with 10 ml of ethyl acetate and filtered again. The filtrate is concentrated and trituration with 10 ml of ethyl acetate gave 0.26 g (yield 92.9%) of a white solid corresponding to the desired compound.

MP 228-230 °C

10 CHN Analysis $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_3\text{Cl}$

Calcd (%) C, 63.52, H, 4.40, N, 12.88

Found (%) C, 63.40, H, 4.41, N, 12.84

Example 207 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide

15 0.2 g of the desired compound (yield 74.1%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 2 4-fluorobenzyl bromide.

mp 210-212 °C,

CHN Analysis. $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_3\text{F}$

Calcd (%) C, 66.02, H, 4.58, N, 13.39

20 Found (%) C, 65.74, H, 4.60, N, 13.03

Example 208 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

25 1.18 g of the desired compound (yield 83.7%) is obtained according to the procedure of Step 1 of the Example 206, but using 3-aminomethyl pyridine.

MS(APCI+) m/z 309.1 (MH⁺),

¹H NMR (400 MHz, DMSO-d₆) δ 3.43 (s, 3H, NCH₃), 4.47 (d, J=5.86 Hz, 2H, NCH₂Ar), 7.31-7.34 (m, 1H, ArH), 7.48 (d, J=8.79 Hz, 1H, ArH), 7.70 (d, J=7.82 Hz, 1H, ArH), 8.20 (dd, J=8.79, 1.95 Hz, 1H, ArH), 8.42-8.43 (m, 1H, ArH), 8.53 (d, J=2.20 Hz, 2H, ArH), 9.30 (t, J=5.62, 1H, ArH), 11.65 (s, 1H, NH),

5

Step 2 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

0.25 g of the desired compound (yield 82.6%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

10

MP 166-168 °C

Anal. Calcd for C₂₃H₁₉N₄O₃F₁ C, 65.79, H, 4.60, N, 13.34 Found C, 65.40, H, 4.40, N, 13.18

Example 209 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide

15

0.25 g of the desired compound (yield 89.3%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 208 and 4-chlorobenzyl bromide.

MP 173-175 °C

20

Anal. (%) Calcd for C₂₃H₁₉N₄O₃Cl₁ C, 62.77, H, 4.48, N, 12.73 Found C, 62.39, H, 4.46, N, 12.71

Example 210 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide

Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide

25

1.29 g of the desired compound (yield 83.8%) is obtained according to the procedure of Example 206, Step 1, but using 3-methoxybenzyl amine.

MP 235-238 °C

Step 2 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide

0.25 g of the desired compound (yield 95%) is obtained according to the procedure of Example 206, Steps 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide

MP 176-178°C

Anal. (%) Calcd for $C_{25}H_{22}N_3O_4F$ C, 67.11, H, 4.96, N, 9.39 Found. C, 66.99, H, 4.99, N, 9.18

Example 211 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide

0.25 g of the desired compound (yield 92%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the Step 1 of Example 210 and 4-chlorobenzyl bromide.

MP 178-180 °C

Anal. (%) Calcd for $C_{25}H_{22}N_3O_4Cl$ C, 64.60, H, 4.79; N, 9.04 Found C, 64.22, H, 4.72, N, 8.84

Example 212 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

Step 1 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

1.00 g of the desired compound (yield 76.9%) is obtained according to the procedure of Example 206, Step 1, but using (2-methoxy-pyridin-4-yl)-methylaniline

MP 215-218 °C

MS(APCI+) m/z 339.1 (MH)

Step 2 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.07 g of the desired compound (yield 26.5%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in the preceding Step 1 and 4-fluorobenzyl bromide.

MP 174-175 °C

Anal. (%) Calcd for $C_{24}H_{21}N_4O_4F$: C, 64.20, H, 4.73, N, 12.48. Found: C, 63.88, H, 4.73, N, 12.08.

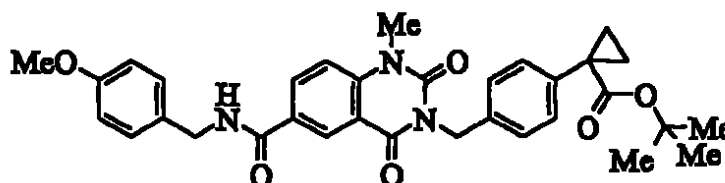
Example 213 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

0.09 g of the desired compound (yield 33%) is obtained according to the procedure of Example 206, Step 2, but using the compound obtained in Step 1 of Example 212 and 4-chlorobenzyl bromide.

MP 169-170 °C

Anal. (%) Calcd for $C_{24}H_{21}N_4O_4Cl$: C, 62.02, H, 4.61, N, 11.98. Found: C, 62.01, H, 5.01, N, 11.70.

Example 214 tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate



0.35 g of the desired compound (yield 67%) is obtained according to the procedure of Example 206, Steps 1 to 2, but using in Step 1 4-methoxy-benzylamine and in Step 2 *tert*-butyl 1-(4-bromomethyl-phenyl)-cyclopropanecarboxylate.

MP 148-149 °C

Anal. (%) Calcd for $C_{33}H_{35}N_3O_6$: C, 68.88, H, 6.24, N, 7.30. Found: C, 68.49, H, 6.29, N, 7.21.

Example 215 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid

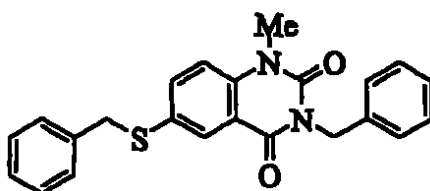
679

To a solution of the compound of Example 214 (0.35 g, 0.61 mmol) in 2 ml of CH_2Cl_2 are added 2 ml of TFA. The yellow solution is stirred at room temperature for 4 hours. The reaction mixture is concentrated and trituration with diethyl ether gives 0.25 g (yield 79%) of a white solid corresponding to the desired compound.

5 MP 179-181°C

Anal. (%) Calcd for $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_6$: C, 66.22, H, 5.35, N, 7.77. Found: C, 66.61, H, 5.40; N, 8.04.

Example 216 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione



10 **Step 1 5-Iodo-2-methylamino-benzoic acid**

To a solution of N-methylanthranilic acid (5.00 g, 3.31 mmol) in 30 ml of acetic acid are added 60 ml of H_2O and I_2 (8.39 g, 3.31 mmol) is added portionwise over a period of 5 minutes. The reaction mixture is stirred at room temperature for 2 days. After 48 hours, the product is filtered and washed with 30 ml of H_2O . The mother liquor is concentrated affording more product.

15

Weight: 7.3 g, Yield = 80%

MP 170-172 °C

MS(APCI+) m/z 276.0 (MH⁺)

Step 2 3-Benzyl-6-iodo-1-methyl-1H-quinazoline-2,4-dione

20 To a mixture of the compound obtained in the preceding Step 1 (0.50 g, 1.9 mmol), isothiocyanate (0.236 g, 1.58 mmol), and $\text{CF}_3\text{CO}_2\text{Ag}$ (0.838 g, 3.80 mmol) is added slowly Et_3N . The reaction mixture is heated at reflux for 1.5 hours. After cooled to room temperature, silver sulfide is filtered and the filtrate is concentrated affording a brown oil. The product is purified by chromatography on silica gel (ethyl acetate/hexane: 20/80) to give 0.300 g (48.0%) of a white solid.

25

MP 149-150°C

MS(APCI+) m/z 391.0 (MH⁺)

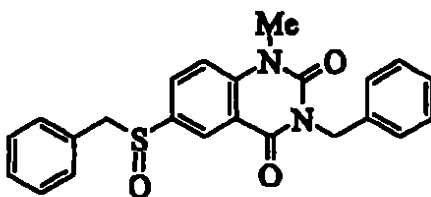
Step 3 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione

To a mixture of KHCO₃ (0.009 g, 0.089 mmol), PPh₃ (0.007 g, 0.027 mmol), n-Bu₄NI (0.033 g, 0.089 mmol), Pd(OAc)₂ (0.002 g, 0.009 mmol), after purging with N₂ for 5 min, are added a solution of the compound of the preceding Step 2 (0.035 g, 0.089 mmol) and butyl-thiocarbamic acid S-benzyl ester (0.020 g, 0.089 mmol) in 5 ml of dioxane at room temperature. The brown solution is heated at 100°C for overnight. After 24 hours, the reaction mixture is cooled to room temperature and diluted with 20 ml of ethyl acetate, filtered through a sheet of celite, washed with H₂O (2x5 ml), concentrated, affording a yellow oil. Trituration with diethyl ether gives 0.025 g (yield 72%) of a yellow solid corresponding to the desired compound.

MP 117-118°C

Anal. (%) Calcd for C₂₃H₂₀N₂O₂S: C, 69.66, H, 5.31, N, 7.06. Found: C, 69.26, H, 5.04, N, 6.93.

Example 217 3-Benzyl-1-methyl-6-phenylmethanesulfinyl-1H-quinazoline-2,4-dione



To a solution of the compound of Example 216 (0.050 g, 0.129 mmol) in 9 ml of anhydrous CH₂Cl₂ is added *m*-chloro-perbenzoic acid (0.029 g, 0.127 mmol) at -5°C. After stirring at -5°C for 3 hours, the reaction mixture is quenched with 20 ml of NaHCO₃ while in the ice-bath. The organic layer is separated and the aqueous is extracted with CH₂Cl₂ (2x20 ml). The combined organic layers are concentrated, affording a yellow oil. The product is purified by chromatography on silica gel (ethyl acetate/hexane 30/70) to give 0.070 g (yield, 33.7%) of a white solid corresponding to the desired compound.

MP 182-183°C

Anal. (%) Calcd for $C_{23}H_{20}N_2O_3S_1$ C, 67.84, H, 5.03, N, 6.88 Found C, 68.13, H, 4.86, N, 6.48

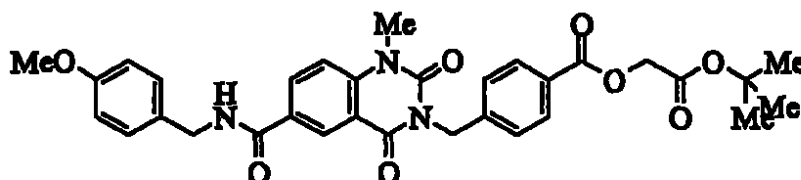
Example 218 3-Benzyl-1-methyl-6-phenylmethanesulfonyl-1*H*-quinazoline-2,4-dione

To a solution of the compound of Example 216 (0.133 g, 0.342 mmol) in 25 ml of anhydrous CH_2Cl_2 is added *m*-chloro-perbenzoic acid (0.153 g, 0.685 mmol) at $-5^\circ C$. After stirring at $-5^\circ C$ for 5 min, the ice-bath is removed and the reaction mixture is stirred at room temperature for 3 hours. The reaction is completed and quenched with 5 ml of saturated $NaHCO_3$. The organic layer is separated and the aqueous is extracted with CH_2Cl_2 (2x20 ml). The combined organic layers are concentrated, affording a yellow oil. Trituration with ethyl acetate gives 0.80 g (yield 56%) of a light yellow solid corresponding to the desired compound.

MP $173-175^\circ C$

Anal. (%) Calcd for $C_{23}H_{20}N_2O_4S_1$ C, 64.73, H, 4.89, N, 6.56 Found C, 64.34, H, 4.72, N, 6.18

Example 219 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazoline-3-ylmethyl]-benzoic acid tert-butoxycarbonylmethyl ester



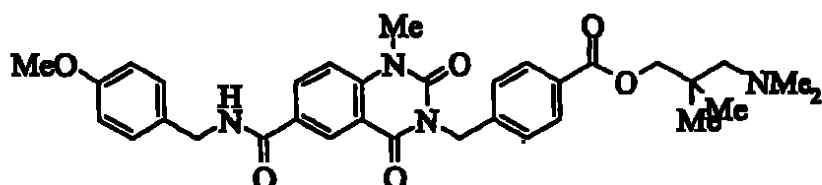
To 0.40 g (0.84 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.13 g (1.0 mmol) followed by tert-butylacetyl chloride 0.18 g (1.18 mmol). The mixture is stirred overnight at room temperature before concentrating in-vacuo, then diluted with ethyl acetate (20 ml). The organic layer is washed with saturated aqueous $NaCl$ solution (2x20 ml), dried $MgSO_4$, and purified by flash chromatography (EtOAc/ hexane eluent) to give 0.11 g (yield 23%) of the desired compound.

MS m/z (APCI, AP+) 588.4 $[M]^+$

180

CHN Analysis (%) $C_{32}H_{33}N_3O_8$ 1.8 H_2O Calcd. C, 61.97, H, 5.61, N, 6.70 Found C, 61.58, H, 5.61, N, 6.70

Example 220 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid dimethylamino-dimethyl-propyl ester

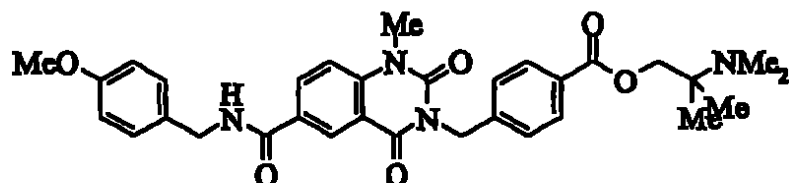


To 0.50 g (1.6 mmol) of compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39 g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by dimethylamino-dimethyl-propan-1-ol 0.27 g (2.1 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried $MgSO_4$. The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl is added. After concentration and solidification in EtOAc, 0.49 g (yield 43%) of the desired compound is obtained.

MS m/z (APCI, AP+) 587.0 $[M]^+$

CHN Analysis (%) $C_{33}H_{38}N_4O_8$ 1.0 HCl 1.2 H_2O Calcd. C, 61.40, H, 6.48, N, 8.68 Found C, 61.01, H, 6.31, N, 8.99

Example 221 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid dimethylamino-methyl-propyl ester



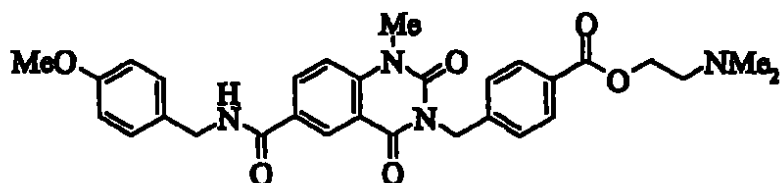
To 0.50 g (1.6 mmol) of the compound of Example 35 in dimethylformamide (20 ml) is added EDAC HCl 0.39 g (2.1 mmol), HOBT 0.28 g (2.1 mmol), followed by

dimethylamino-methyl-propan-1-ol 0.24 g (2.1 mmol) The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2x20 ml) The combined organic layers are washed with saturated aqueous NaCl solution (4 x 20 ml), and dried MgSO₄ The crude product is dissolved in EtOAc/MeOH and saturated ethereal HCl is added. After concentration and solidification in EtOAc, 0.21 g (yield: 21%) of the desired compound is obtained.

MS m/z (APCI, AP+) 573 2 [M]⁺

CHN Analysis (%). C₃₂H₃₆N₄O₆ 1.0 HCl 0.48 H₂O Calcd C, 62.22, H, 6.19, N, 9.07 Found C, 61.82, H, 6.00, N, 9.16

10 **Example 222 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester**



To 0.73 g (1.5 mmol) of the compound of Example 35 in dimethylformamide (10 ml) is added EDAC HCl 0.38g (2.0 mmol), HOBT 0.27 g (2.0 mmol), followed by dimethylamino-propan-1-ol 0.18 g (2.0 mmol) The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml) The combined organic layers are washed with saturated aqueous NaCl solution (2 x 20 ml), and dried MgSO₄ the crude product is solidified in EtOAc to give 0.49 g (yield: 60%) of the desired compound.

20 MS m/z (APCI, AP+) 545 3 [M]⁺

CHN Analysis (%) C₃₀H₃₂N₄O₆ 0.25 H₂O Calcd C, 65.62, H, 5.97, N, 10.20 Found C, 65.62, H, 5.92, N, 10.23

Example 223 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid chloromethyl ester

182

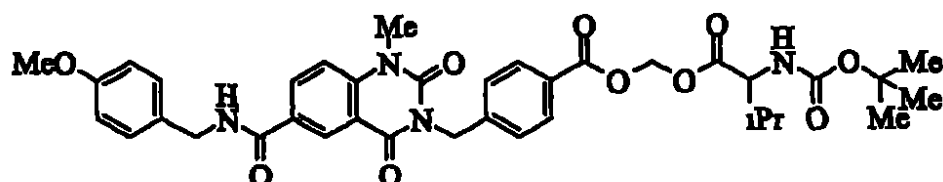


To 1.0 g (2.1 mmol) of the compound of Example 35 in dimethylformamide (15 ml) is di-isopropylethylamine 0.47 g (3.6 mmol) followed by chloroiodomethane 1.86 g (10.5 mmol). The mixture is stirred overnight at room temperature before diluting with ethyl acetate (20 ml). The organic layer is washed with water (1x10 ml), saturated aqueous NaCl solution (2x10 ml), and dried MgSO₄. After solidification in ether 0.29 g (yield, 26%) of the desired compound is obtained.

MS m/z (APCI, AP+) 522.2 [M]⁺

CHN Analysis (%) C₂₇H₂₄ClN₃O₆ Calcd. C, 62.13, H, 4.63, N, 8.05 Found. C, 62.08, H, 4.61, N, 7.95

Example 224 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid 2-tert-butoxycarbonylamino-3-methyl-1-butanoyloxymethyl ester ester



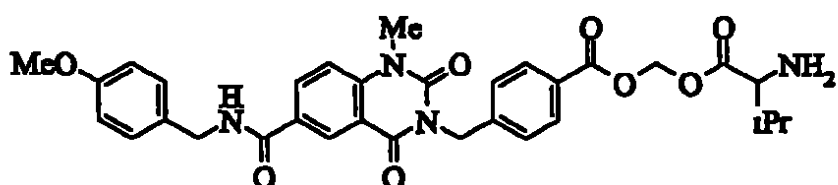
To 0.39 g (0.75 mmol) of the compound of Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.12 g (0.96 mmol) followed by t-butoxycarbonyl-leucine 0.21 g (0.96 mmol). The mixture is stirred overnight at 60-70°C for 12 hours, cooled and diluted with ethyl acetate (20 ml). The organic layer is washed with water (1 x 10 ml), 5% aqueous NaHCO₃ solution (1x10 ml), saturated aqueous NaCl (1x10 ml), dried MgSO₄, and purified by flash chromatography (EtOAc/ hexane eluent) to give 0.14 g (yield 25%) of the desired compound.

MS m/z (APCI, AP+) 701.3 [M - Boc]

CHN Analysis (%) C₃₇H₄₂N₄O₁₀ Calcd. C, 61.97, H, 5.61, N, 6.70 Found. C, 61.58, H, 5.61, N, 6.70

CB2

Example 225. 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-amino-3-methyl-butanoyloxymethyl ester hydrochloride

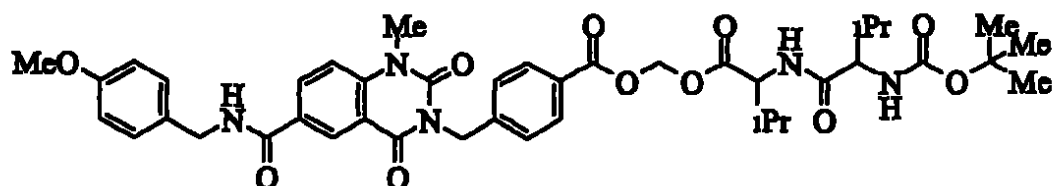


5 To 0.14 g (0.19 mmol) of the compound of Example 224 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.039 g (yield 30%) of the desired compound is obtained.

MS m/z (APCI, AP^+) 603.2 $[M]^+$

10 CHN Analysis (%): $C_{37}H_{42}N_4O_{10}$ Calcd C, 61.97, H, 5.61, N, 6.70 Found C, 61.58, H, 5.61, N, 6.70

Example 226. 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester



15

Step 1: 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid methyl ester

To 1.3 g (5.9 mmol) of t-butoxycarbonyl-leucine in dimethylformamide (15 ml) is added EDAC HCl 1.4g (7.1 mmol), HOBT 0.95 g (7.1 mmol), followed by NH_2 -Leu-OMe 1.0 g (5.9 mmol). The mixture is stirred overnight at room temperature before adding water (20 ml) and extracting with ethyl acetate (2 x 20 ml). The combined organic layers are washed

20

with 10% aqueous Na_2CO_3 (1 x 10 ml), saturated aqueous NaCl solution (2 x 20 ml), and dried MgSO_4 . A solidification in ether gives 1.05 g (yield 53%) of the desired compound.

MS m/z (APCI, AP+) 331.2 $[\text{M}]^+$

CHN Analysis (%) $\text{C}_{16}\text{H}_{30}\text{N}_2\text{O}_5$ Calcd C, 58.16, H, 9.15, N, 8.48 Found C, 58.32, H, 9.24, N, 8.51

Step 2 2-(2-tert-Butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butyric acid

To 0.4 g (1.2 mmol) of the compound obtained in the preceding step 1, in 3:1:1 methanol/water/THF (10 ml) is added $\text{LiOH} \cdot \text{H}_2\text{O}$, 0.06 g (1.44 mmol). The mixture is stirred overnight at room temperature. Partitioned between water (20 ml) and ethyl acetate (30 ml). The layers are separated and the aqueous layer made acidic with 2 M HCl . The product is extracted with EtOAc (2 x 20 ml), washed with saturated aqueous NaCl solution (1 x 20 ml), and dried MgSO_4 . A solidification in ether gives 0.22 g (yield 58%) of the desired compound.

MS m/z (APCI, AP+) 317.2 $[\text{M}]^+$

CHN Analysis (%) $\text{C}_{15}\text{H}_{28}\text{N}_2\text{O}_5$ Calcd C, 56.94, H, 8.92, N, 8.85 Found C, 56.72, H, 8.89, N, 8.64

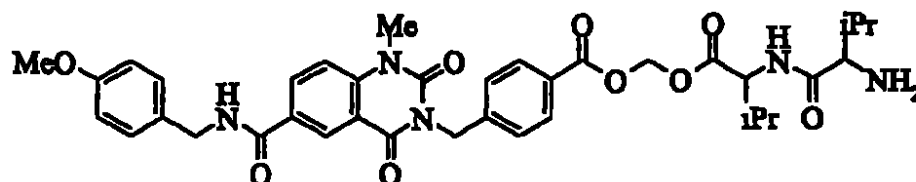
Step 3 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoyloxymethyl ester

To 0.29 g (0.56 mmol) of the compound obtained in Example 223 in dimethylformamide (10 ml) is added di-isopropylethylamine 0.092 g (0.72 mmol) followed by compound obtained in the preceding Step 2, 0.23 g (0.72 mmol) then NaI (cat.). The mixture is stirred overnight at 50°C for 18 hours. Cool and dilute with water and extract with ethyl acetate (2 x 20 ml). The combined organic layer are washed with saturated aqueous NaHCO_3 solution (1 x 10 ml), saturated aqueous NaCl (3 x 10 ml) and dried MgSO_4 . A solidification in a mixture of EtOAc /hexane gives 0.27 g (yield 63%) of the desired compound.

MS m/z (APCI, AP+) 800.4 $[\text{M} - \text{Boc}]^+$

CHN Analysis (%) $\text{C}_{37}\text{H}_{42}\text{N}_4\text{O}_{10}$ Calcd C, 62.91, H, 6.41, N, 8.73 Found C, 62.59, H, 6.44, N, 8.39

Example 227: 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]- benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester



5 To 0.25 g (0.31 mmol) of compound of the Example 226 in dioxane (10 ml) is added 1.0 M HCl in ether (10 ml). HCl gas is bubbled through for 2 minutes then mixture is stirred 90 minutes at room temperature. After concentration and trituration in EtOAc, 0.12 g (yield 55%) of the desired compound is obtained.

MS m/z (APCI, AP+): 702.0 $[M]^+$

10 CHN Analysis (%) $C_{37}H_{43}N_5O_9$, Calcd: C, 63.33, H, 6.18, N, 9.98. Found: C, 62.99, H, 6.06, N, 9.72.

Examples 228 to 345.

These compounds were obtained according to the procedure described in the Example 168 followed by the procedure of the Example 169.

- 15 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
 20 pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

5 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

10 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

15 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

20 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

25 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

30 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,

- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 5 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide,
- 10 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 15 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
20 pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 25 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
30 pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 5 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
10 pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 15 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
20 pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 25 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
30 pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,

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- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 5 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 10 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 15 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
20 pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 25 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
30 pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 5 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 10 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 15 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
20 pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 25 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
30 pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

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- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 5 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 10 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-[2-(4-Fluoro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 15 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 20 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 25 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,
- 30 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide,

5 3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-[2-(4-Bromo-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

10 3-[2-(4-Chloro-phenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

15 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

20 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

25 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide,

and 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]
30 pyrimidine-6-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide

Examples 345 to 461

These compounds were obtained according to the procedure described for Example 131

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

10 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

15 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

20 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

25 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

30 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

5 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

10 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-hydroxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

15 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

20 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

25 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methylamino-pyridazin-4-ylmethyl)-amide,

30 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,

- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 10 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
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- 15 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 20 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 25 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,
- 30 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

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3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-hydroxy-pyridazin-4-ylmethyl)-amide,

5 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

10 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

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15 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

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3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

25 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

30 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,

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- 3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 5 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 10 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-ethoxy-pyridazin-4-ylmethyl)-amide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
- 15 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
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- 25 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methylamino-pyridazin-4-ylmethyl)-amide,
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- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,
- 30 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

5 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

10 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-methyl-pyridazin-4-ylmethyl)-amide,

15 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

20 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

25 3-(3-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

30 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(4-Iodo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-ethoxy-pyridazin-4-ylmethyl)-amide,

3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

5 3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

10 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

15 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-amino-pyridazin-4-ylmethyl)-amide,

20 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3,4-Dichloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

25 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

30 3-(3-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(3-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide,

5 and 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methyl-pyridazin-4-ylmethyl)-amide.

EXAMPLE 462

Evaluation of the *in vitro* activity of the compounds of formula (I) according to the invention

10 The ability of the compounds of formula (I) of the invention to inhibit matrix metalloprotease 13 was evaluated by measuring their IC₅₀ value (concentration required to inhibit 50% of the enzymatic activity) according to the protocol described below

MMP13CD Thiopeptolide Assay Proteolysis of the thiopeptolide substrate Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OBt is used as the primary screen to determine IC₅₀ values for

15 MMP13 inhibitors A 100 µl reaction contains 50 mM HEPES, 10 mM CaCl₂, pH 7.0 (RT), 1 mM 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), 100 µM substrate, inhibitor in 2.0% DMSO and 2.5 nM human collagenase-3 catalytic domain enzyme. Inhibitors are screened from 100 µM to 0.5 nM. The change in absorbance at 405 nm is monitored on a

20 microplate reader at room temperature continuously for 10-15 minutes. Percentage of control velocity in inhibited treatments is plotted against inhibitor concentration to calculate IC₅₀ values.

Table 1

Example	IC ₅₀ (µM)	Example	IC ₅₀ (µM)
1	0.193	26	0.009

2	0 183	27	1 7
3	0 021	28	0 017
4	1 87	29	0 003
5	0 366	30	0 026
6	0 049	31	0 157
7	0 167	32	0 6
8	1 32	33	0 75
9	0 005	34	0 004
10	0 057	35	0 001
11	2 25	36	0 028
12	0 042	37	0 029
13	0 012	38	0 031
14	0 051	39	0 011
15	0 7	40	0 004
16	0 015	41	0 007
17	0 009	42	0 0025
18	0 01	43	1.21
20	0 051	44	0 016
21	0 3	45	0 007
22	0 096	46	0 096
23	0 029	47	0 062
24	0 009	48	0 014
25	0 028		

Examination of the results of Table 1 shows that the products of the invention tested in the assay effectively inhibit matrix metalloprotease 13

The protocol described above was also used to measure the activity of the compounds of the invention against MMP1, MMP2, MMP3, MMP7, MMP9, MMP12 and MMP14. The IC₅₀ values obtained on these MMPs were often greater than 100 μ M. These results indicate that the compounds of the invention are selective MMP13 inhibitors

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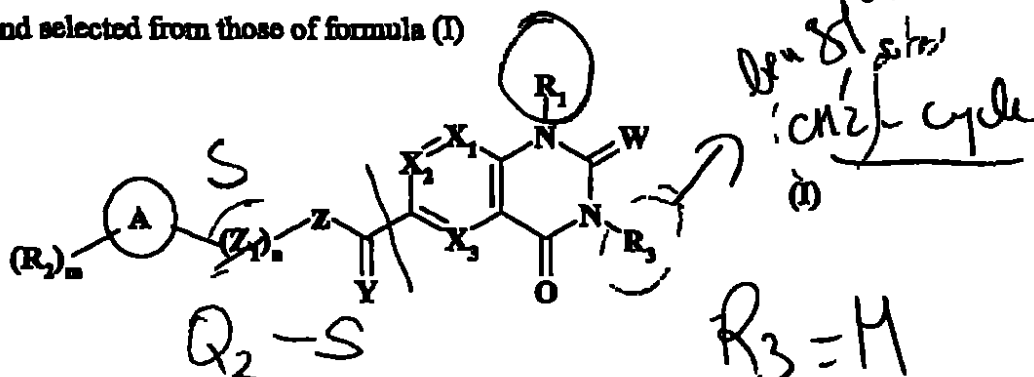
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Claims

I-A compound selected from those of formula (I)



in which.

5 R_1 represents a group selected from

- hydrogen, amino,
- (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, mono (C_1-C_6) alkylamino (C_1-C_6) alkyl,

10 di (C_1-C_6) alkylamino (C_1-C_6) alkyl, aryl, aryl (C_1-C_6) alkyl, heterocycle, and 3- to 6-membered cycloalkyl (C_1-C_6) alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, (C_1-C_6) alkyl, cyano, halo (C_1-C_6) alkyl, $C(=O)OR_4$, OR_4 and SR_4 , in which R_4 represents hydrogen or (C_1-C_6) alkyl,

W represents an oxygen atom, a sulphur atom, or a group $=N-R'$, in which R' represents (C_1-C_6) alkyl, hydroxyl, or cyano,

15 X_1 , X_2 and X_3 represent, independently of each other, a nitrogen atom or a group $-C-R_6$ in which R_6 represents a group selected from hydrogen, (C_1-C_6) alkyl, amino, mono (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, hydroxyl, (C_1-C_6) alkoxy, and halogen, with the proviso that not more than two of the groups X_1 , X_2 and X_3 simultaneously represent a nitrogen atom,

20 Y represents a group selected from oxygen atom, sulphur atom, $-NH$, and $-N(C_1-C_6)$ alkyl,

 Z represents

- an oxygen atom, a sulphur atom,

• or a group $-NR_7$ in which R_7 represents a group selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl, and heteroaryl, and

• when Y is an oxygen atom, a sulphur atom, or a group $-N(C_1-C_6)$ alkyl, Z optionally represents a carbon atom which is unsubstituted or substituted with a (C_1-C_6) alkyl, an aryl, an aryl (C_1-C_6) alkyl, an aromatic or non-aromatic heterocycle or a cycloalkyl,

n is an integer from 1 to 8 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 and R_9 , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, halogen, amino, OR_4 , SR_4 or $C(=O)OR_4$ in which R_4 represents a hydrogen or (C_1-C_6) alkyl, and

• when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,

• and/or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,

• and when one of the carbon atoms in the hydrocarbon chain Z_1 is replaced with a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, then the group $-C(=Y)-Z-$ optionally may be absent in the general formula (I),

A represents a group selected from

• aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and

• bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,

m is an integer from 0 to 7 inclusive,

the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, NO_2 , SCF_3 , $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, SOR_{10} , $-SO_2R_{10}$,

$-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_3(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$,
 $-X_3(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

- X_3 represents a group selected from oxygen, sulphur optionally substituted by one or two oxygen atoms, and nitrogen substituted by hydrogen or (C_1-C_6) alkyl,

5 • k is an integer from 0 to 3 inclusive,

- R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,

10 • X_4 represents a group selected from single bond, $-CH_2-$, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C_1-C_6) alkyl group,

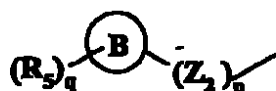
15 • R_{12} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl and amino, and when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur;

R_3 represents a group selected from

- ~~hydrogen,~~

20 • (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, cyano, halo (C_1-C_6) alkyl, cycloalkyl, $-C(=O)NR_{10}R_{11}$, $-C(=O)OR_{10}$, OR_{10} , and SR_{10} , in which R_{10} and R_{11} , which may be identical or different, represent hydrogen or (C_1-C_6) alkyl,

- and the group of formula



25 ✓ in which p is an integer from 0 to 8 inclusive,

- ✓ Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, phenyl, halo (C_1-C_6) alkyl, halogen, amino, OR_4 , SR_4 and $-C(=O)OR_4$ in which R_4 represents hydrogen or (C_1-C_6) alkyl, and
- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
 - and/or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl, or a carbonyl group,
- 10 ✓ B represents a group selected from.
- an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, and
 - a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- 15 ✓ q is an integer from 0 to 7 inclusive,
- ✓ the group(s) R_5 , which may be identical or different, is (are) selected from
- 20 (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_kR_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-C(=O)O-(CH_2)_{k2}-C(=O)OR_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, $-R_{19}-C(=O)OR_{15}$, $-X_8-R_{20}$, and $-C(=O)-R_{21}-NR_{15}R_{16}$ in which
- 25 - X_7 represents a group selected from oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by a hydrogen atom or a (C_1-C_6) alkyl group,
- k is an integer from 0 to 3 inclusive,

- k1 is an integer from 0 to 2 inclusive,
 - k2 is an integer from 1 to 4 inclusive,
 - R₁₅, R₁₆ and R₁₇, which may be identical or different, are selected from hydrogen and (C₁-C₆)alkyl,
- 5
- R₁₈ represents a group selected from (C₁-C₆)alkyl, -R₂₁-NR₁₅R₁₆, -R₂₁-NR₁₅-C(=O)-R₂₁-NR₁₆R₁₇, and -C(=O)O-R₂₁-NR₁₅R₁₆ in which R₂₁ represents a linear or branched (C₁-C₆)alkylene group, and R₁₅, R₁₆ and R₁₇ are as defined hereinbefore,
 - R₁₉ represents a (C₃-C₆)cycloalkyl group,
- 10
- X₆ represents a group selected from single bond, -CH₂-, oxygen atom, sulphur atom optionally substituted by one or two oxygen atoms, and nitrogen atom substituted by hydrogen atom or (C₁-C₆)alkyl group,
- 15
- R₂₀ represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C₁-C₆)alkyl, halogen, hydroxyl, oxo, cyano, tetrazole, amino, and -C(=O)OR₄ wherein R₄ represents hydrogen or (C₁-C₆)alkyl, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- 20
- with the proviso that when X₁ represents a nitrogen atom, X₂ cannot represent a carbon atom substituted with a methyl group or with NH-CH₃, optionally, the racemic forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable salts thereof.

2- A compound of formula (I) according to Claim 1 characterized in that

- R_1 represents hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl or 3- to 6-membered cycloalkyl (C_1-C_6) alkyl,
 - W represents an oxygen atom or a sulphur atom,
 - X_1 represents a nitrogen atom or $-C-R_6$ in which R_6 represents a hydrogen atom,
 - 5 • X_2 and X_3 represent each $-C-R_6$ in which R_6 represents a hydrogen atom,
 - Y represents an oxygen atom,
 - Z represents an oxygen atom or $-NR_7$ in which R_7 represents a hydrogen atom,
- optionally, the racemic forms thereof, isomers thereof, N-oxides thereof, and the pharmaceutically acceptable salts thereof

- 10 3- A compound of formula (I) according to Claim 1 characterized in that.
n is an integer from 1 to 6 inclusive,

Z_1 represents $-CR_8R_9$ wherein R_8 represents a hydrogen atom and R_9 represents a hydrogen atom or a methyl group, and

- 15 - when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains a double bond,
- or, one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, or a sulphur atom which is unsubstituted or substituted with one or two oxygens,

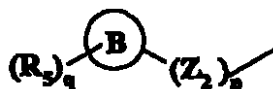
- 20 A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, piperidyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

m is an integer from 0 to 7 inclusive,

- the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$,
25 $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$,
 $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

- ✓ X_3 represents O, S or NH,
 - ✓ k is an integer from 0 to 3 inclusive,
 - ✓ R_{10} and R_{11} , identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
 - ✓ X_4 represents $-CH_2-$, or an oxygen atom,
 - 5 ✓ R_{12} represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl and amino,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof

- 10 4- A compound of formula (I) according to Claim 1 characterized in that:
 R_3 represents hydrogen, (C_1-C_6) alkyl or the group of formula.



- in which p is an integer from 0 to 3 inclusive,
- Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, methyl, or phenyl, and
- 15 • when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,
- or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl, or a carbonyl group,
- 20 • B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl, and indolyl,
- 25 • q is an integer from 0 to 3 inclusive,

- the group(s) R_5 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$ in which

- X_7 is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

5- A compound of formula (I) according to Claim 1 characterized in that:

R_1 represents a group selected from

- hydrogen, amino,
- (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, mono (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, aryl, aryl (C_1-C_6) alkyl, heterocycle, and 3- to 6-membered cycloalkyl (C_1-C_6) alkyl, these groups being unsubstituted or substituted with one or more groups, which may be identical or different, selected from amino, (C_1-C_6) alkyl, cyano, halo (C_1-C_6) alkyl, $C(=O)OR_4$, OR_4 and SR_4 , in which R_4 represents hydrogen or (C_1-C_6) alkyl,

W represents an oxygen atom, a sulphur atom, or a group $=N-R'$, in which R' represents (C_1-C_6) alkyl, hydroxyl, or cyano,

X_1 represents a nitrogen atom or a group $-C-R_6$ in which R_6 represents a hydrogen atom,

X_2 and X_3 represent, independently of each other, a group $-C-R_6$ in which R_6 represents a group selected from hydrogen, (C_1-C_6) alkyl, amino, hydroxyl and halogen,

Y represents an oxygen atom,

Z represents an oxygen atom, or a group $-NR_7$ in which R_7 represents a group selected from hydrogen, and (C_1-C_6) alkyl,

n is an integer from 1 to 6 inclusive,

- 5 Z_1 represents $-CR_8R_9$ wherein R_8 and R_9 , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl and hydroxyl, and
- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one or more multiple bonds,
 - or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an
- 10 oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzofurazanyl, 2,1,3-benzothiadiazolyl, and indolyl,

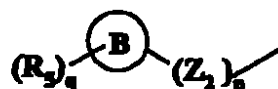
- 15 m is an integer from 0 to 3 inclusive,

the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_5(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_5(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

- 20
- X_3 represents O, S or NH,
 - k is an integer from 0 to 3 inclusive,
 - R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
 - X_4 represents $-CH_2-$, or an oxygen atom,

• R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C₁-C₆)alkyl, halogen, and hydroxyl,

R_3 represents a group selected from hydrogen, (C₁-C₆)alkyl, and the group of formula



- 5 - in which p is an integer from 0 to 6 inclusive,
- Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, (C₁-C₆)alkyl, and hydroxy, and
- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one or more multiple bonds,
- 10 • or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C₁-C₆)alkyl,
- B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl, and indolyl,
- 15 - q is an integer from 0 to 3 inclusive,
- the group(s) R_3 , which may be identical or different, is (are) selected from (C₁-C₆)alkyl, halogen, CN, NO₂, CF₃, OCF₃, $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_6-R_{20}$ in which
- 20 • X_7 is S, O or NH,
- 25 • k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C₁-C₆)alkyl,

- X_6 represents a single bond, $-\text{CH}_2-$, an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
 - R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.
- 6- A compound of formula (I) according to Claim 1 characterized in that
- R_1 represents a group selected from hydrogen, mono (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, (C_1-C_6) alkyl, (C_3-C_6) alkenyl, (C_3-C_6) alkynyl, aryl, aryl (C_1-C_6) alkyl, and 3- to 6-membered cycloalkyl (C_1-C_6) alkyl,
- W represents an oxygen atom, or a sulphur atom,
- X_1 represents a nitrogen atom or a $-\text{CH}$ group,
- X_2 and X_3 represent a $-\text{CH}$ group,
- Y represents a group selected from oxygen atom, sulphur atom, $-\text{NH}$, and $-\text{N}(\text{C}_1-\text{C}_6)$ alkyl,
- Z represents an oxygen atom or a $-\text{NH}$ group,
- n is an integer from 1 to 3 inclusive,
- Z_1 represents $-\text{CR}_8\text{R}_9$ wherein R_8 and R_9 , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl and hydroxy, and
- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one double bond,

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• or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a $-NH$ group,

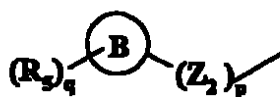
A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,

m is an integer from 0 to 3 inclusive,

the group(s) R_2 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, $-CN$, $-CF_3$, $-OCF_3$, $-NR_{10}R_{11}$, $-OR_{10}$, $-SR_{10}$, $-SO_2R_{10}$, $-(CH_2)_kSO_2NR_{10}R_{11}$, $-X_3(CH_2)_kC(=O)OR_{10}$, $-(CH_2)_kC(=O)OR_{10}$, $-X_3(CH_2)_kC(=O)NR_{10}R_{11}$, $-(CH_2)_kC(=O)NR_{10}R_{11}$, and $-X_4-R_{12}$ in which

- X_3 represents O, S or NH,
- k is an integer from 0 to 3 inclusive,
- R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- X_4 represents $-CH_2-$, or an oxygen atom,
- R_{12} represents phenyl which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6) alkyl, halogen, and hydroxyl,

R_3 represents a group selected from methyl and the group of formula



- in which p is an integer from 0 to 3 inclusive,
- Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, (C_1-C_6) alkyl, and hydroxy, and
- when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,

- or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,
- 5 - B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, 1,3-benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, 2,1,3-benzothiadiazolyl, benzofurazanyl, naphthyl and indolyl,
- q is an integer from 0 to 3 inclusive,
- the group(s) R_5 , which may be identical or different, is (are) selected from
- 10 (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, $-(CH_2)_kC(=O)NR_{15}R_{16}$, and $-X_6-R_{20}$ in which
- 15 • X_7 is S, O or NH,
- k is an integer from 0 to 3 inclusive,
- k_1 is an integer from 0 to 2 inclusive,
- k_2 is an integer from 1 to 4 inclusive,
- R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen
- 20 and (C_1-C_6) alkyl,
- X_6 represents a single bond, CH_2 , an oxygen atom or a sulphur atom which is unsubstituted or substituted with one or two oxygen atom,
- R_{20} represents an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring, which is unsubstituted or substituted with one or more groups,
- 25 which may be identical or different, selected from (C_1-C_6) alkyl, halogen, hydroxyl, and amino, and, when the ring is heterocyclic, it comprises from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur,
- optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

30 7- A compound of formula (I) according to Claim 1 characterized in that

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R_1 represents hydrogen, (C₁-C₆)alkyl, (C₃-C₆)alkenyl, aryl(C₁-C₆)alkyl, 3- to 6-membered cycloalkyl(C₁-C₆)alkyl,

W represents an oxygen atom,

X_1 represents -CH group or nitrogen atom, and X_2 and X_3 represent each -CH group,

5 Y represents an oxygen atom,

Z represents an oxygen atom or a -NH group,

n is an integer from 1 to 3 inclusive,

Z_1 represents -CR₈R₉, wherein R₈ and R₉, independently of each other, represent a group selected from hydrogen and methyl, and

- 10
- when n is greater than or equal to 2, the hydrocarbon chain Z_1 optionally contains one double bond,
 - or one of the carbon atoms in the hydrocarbon chain Z_1 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, or a -NH group,

15 A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,

m is an integer from 0 to 3 inclusive,

the group(s) R_2 , which may be identical or different, is (are) selected from (C₁-C₆)alkyl, halogen, -CN, -CF₃, -OCF₃, -NR₁₀R₁₁, -OR₁₀, -SR₁₀, -SO₂R₁₀, -(CH₂)_kSO₂NR₁₀R₁₁,

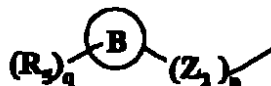
20 -X₃(CH₂)_kC(=O)OR₁₀, -(CH₂)_kC(=O)OR₁₀, -X₃(CH₂)_kC(=O)NR₁₀R₁₁, and -(CH₂)_kC(=O)NR₁₀R₁₁, in which

- X₃ represents O, S or NH,
- k is an integer from 0 to 3 inclusive,

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- R_{10} and R_{11} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,

R_3 represents the group of formula



- 5 - in which p is an integer from 0 to 3 inclusive,
- Z_2 represents $-CR_{13}R_{14}$ wherein R_{13} and R_{14} , independently of each other, represent a group selected from hydrogen, and methyl, and
 - when p is greater than or equal to 2, the hydrocarbon chain Z_2 optionally contains one double bond,
- 10 • or one of the carbon atoms in the hydrocarbon chain Z_2 may be replaced with an oxygen atom, a sulphur atom which is unsubstituted or substituted with one or two oxygen atoms, a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6) alkyl,
- B represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, and 1,3-benzodioxolyl,
- 15 - q is an integer from 0 to 3 inclusive,
- the group(s) R_3 , which may be identical or different, is (are) selected from (C_1-C_6) alkyl, halogen, CN, NO_2 , CF_3 , OCF_3 , $-(CH_2)_kNR_{15}R_{16}$, $-N(R_{15})C(=O)R_{16}$, $-N(R_{15})C(=O)OR_{16}$, $-N(R_{15})SO_2R_{16}$, $-N(SO_2R_{15})_2$, $-OR_{15}$, $-S(O)_{k1}R_{15}$, $-SO_2-N(R_{15})-(CH_2)_{k2}-NR_{16}R_{17}$, $-(CH_2)_kSO_2NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)OR_{15}$, $-(CH_2)_kC(=O)OR_{15}$, $-C(=O)O-(CH_2)_{k2}-NR_{15}R_{16}$, $-X_7(CH_2)_kC(=O)NR_{15}R_{16}$, and $-(CH_2)_kC(=O)NR_{15}R_{16}$, in which
 - X_7 is S, O or NH ,
 - k is an integer from 0 to 3 inclusive,
 - $k1$ is an integer from 0 to 2 inclusive,
 - $k2$ is an integer from 1 to 4 inclusive,
 - R_{15} , R_{16} and R_{17} , which may be identical or different, are selected from hydrogen and (C_1-C_6) alkyl,
- 20
- 25

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

5 **8-** A compound of formula (I) according to Claim 1 characterized in that R_1 represents a hydrogen atom or a (C_1-C_6) alkyl group, optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

9- A compound of formula (I) according to Claim 1 characterized in that
W represents an oxygen atom,
Y represents an oxygen atom,
Z represents a NH group,
10 **Z_1** represents a methylene group,
and n is equal to one,
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof

15 **10-** A compound of formula (I) according to Claim 1 characterized in that
 X_1 represents a -CH group or a nitrogen atom,
and X_2 and X_3 represent each a -CH group,
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

20 **11-** A compound of formula (I) according to Claim 1 characterized in that
 X_1 and X_3 represent each a -CH group,
and X_2 represents a -CH group or a nitrogen atom,
optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

25 **12-** A compound of formula (I) according to Claim 1 characterized in that
 X_1 and X_3 represent each a -CH group,
and X_2 represents a nitrogen atom,

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optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof

13- A compound of formula (I) according to Claim 1 characterized in that

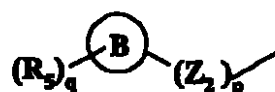
A represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

m is equal to 0 or 1,

and R₂ represents a group selected from (C₁-C₆)alkoxy, hydroxy, halogen, and (C₁-C₆)thioalkoxy,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof

14- A compound of formula (I) according to Claim 1 characterized in that R₃ represents a group of formula



in which

p is equal to 1,

Z₂ represents a methylen group,

B represents a group selected from phenyl, pyridyl, 1,3-benzodioxolyl, and benzofurazanyl,

q is an integer from 0 to 2 inclusive,

and R₅ represent(s) a group selected from halogen, CN, -(CH₂)_kNR₁₅R₁₆, -S(O)_{k1}R₁₅, -(CH₂)_kSO₂NR₁₅R₁₆, -(CH₂)_kC(=O)OR₁₅, -(CH₂)_kC(=O)NR₁₅R₁₆, and -X₆-R₂₀, in which

- k is an integer from 0 to 1 inclusive,

- k1 is an integer from 0 to 2 inclusive,

- R₁₅ and R₁₆, which may be identical or different, are selected from hydrogen and (C₁-C₆)alkyl,

- X₆ represents a bond,

- -R₂₀ represents a 5-membered heterocyclic ring comprising from 3 to 4 heteroatoms selected from oxygen and nitrogen and optionally substituted with a methyl group or an oxo group,

optionally, the racemic forms thereof, isomers thereof, N-oxydes thereof, and the pharmaceutically acceptable salts thereof.

15- A compound of formula (I) according to Claim 1, which is

- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
- 5 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (4-pyridylmethyl) amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-thienylmethyl) amide,
- 10 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (3-pyridylmethyl) amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzyl amide,
- 15 - 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-chlorobenzyl amide,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methylbenzyl amide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 20 (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide ,
- Methyl 4-([1-(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-yl) methanoyl]amino)methyl)benzoate,
- 25 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-hydroxy-3-methoxybenzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy benzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 30 (4-pyridylmethyl)amide,
- 1-Methyl-2,4-dioxo-3-phenethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid

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- (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Methoxybenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
(benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide,
 - 3-(1-Naphth-1-ylethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 2,4-Dioxo-3-(pyrid-4-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide ,
 - 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
 - 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid benzylamide,
 - 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 1-Methyl-2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide ,
 - 3-(4-Chlorobenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 3-Benzyl-1-cyclopropylmethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic

- acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-Benzyl-1-isobutyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
 - 1-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
- 5 (benzo[1,3]dioxol-5-ylmethyl)amide,
- Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H]-quinazolin-3-ylmethyl]-benzoic acid,
- 10 - 1-Methyl-2,4-dioxo-3-((E)-3-phenylallyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
 - Benzyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
 - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 15 - 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
 - Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro
- 20 quinazoline-6-carboxylate,
- Benzyl 1-benzyl-2,4-dioxo-3-pyrid-4-ylmethyl-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
 - 4-Pyridylmethyl 2,4-dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 25 - 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- Benzyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate
 - 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate,
- 30 - 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-

- ylmethyl]-benzoic acid,
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
 - 5 carboxylic acid 4-methoxy-benzylamide,
 - 3-Allyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-2,4-dioxo-3-(2-pyrrol-1-yl-ethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 10 - 1-Methyl-2,4-dioxo-3-prop-2-ynyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-(3-methyl-but-2-enyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-2,4-dioxo-3-pyridin-2-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic
 - 15 acid 4-methoxy-benzylamide,
 - 3-Carbamoylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-2,4-dioxo-3-pyridin-3-ylmethyl-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 20 - 1-Methyl-3-(1-methyl-piperidin-3-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(3-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic
 - 25 acid 4-methoxy-benzylamide,
 - 3-(2-Methoxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(3-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 30 - 3-Cyclopropylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-

carboxylic acid 4-methoxy-benzylamide,

- 3-Cyclohexylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-2,4-dioxo-3-(3-phenyl-propyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 5 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-[2-(4-Diethylamino-phenyl)-2-oxo-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 10 - Ethyl [6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-acetate,
- 3-(2-Hydroxy-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 3-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionate,
- 15 - 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-propionic acid,
- Ethyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyrate,
- 20 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-butyric acid,
- Methyl {4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetate,
- {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-acetic acid,
- 25 - 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-3-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 30 - 1-Methyl-2,4-dioxo-3-[(E)-3-(pyridin-4-yl)-allyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydroquinazoline-6-

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- 23/2 carboxylic acid 4-methoxy-benzylamide,
 /- 3-(4-Methanesulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-
 carboxylic acid 4-methoxy-benzylamide,
 - 3-(4-Dimethylsulfonyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-
 5 carboxylic acid 4-methoxy-benzylamide,
 - 3-[4-(2-Dimethylamino-ethylsulfonyl)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-
 -quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-(4-methylsulfonyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-
 carboxylic acid 4-methoxy-benzylamide,
 10 - Methyl 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-
 quinoxalin-3-ylmethyl]-benzoate,
 - 3-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-
 ylmethyl]-benzoic acid,
 - (E) Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-
 15 quinoxalin-3-yl]-but-2-enoate,
 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-
 yl]-but-2-enoic acid,
 - Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-
 quinoxalin-3-ylmethyl]-furan-2-carboxylate,
 20 - 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-
 ylmethyl]-furan-2-carboxylic acid,
 - Methyl 5-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-
 quinoxalin-3-ylmethyl]-thiophene-2-carboxylate,
 - 5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-
 25 ylmethyl]-thiophene-2-carboxylic acid,
 - 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic
 acid 4-methoxy-benzylamide,
 - 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic
 acid 4-methoxy-benzylamide,
 30 - 3-(4-Dimethylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-
 carboxylic acid 4-methoxy-benzylamide,
 - 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-

- carboxylic acid 4-methoxy-benzylamide,
- 3-[4-(*NN*-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-Benzofurazan-5-ylmethyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
 - 5 carboxylic acid 4-methoxy-benzylamide,
 - 3-[2-(4-Fluorophenoxy)-ethyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(2-Benzenesulfonyl-ethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 10 - 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy benzylamine,
 - 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-
 - 15 quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - Methyl 2-chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
 - 20 - 2-Chloro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
 - 1-Methyl-3-[4-(1-methyl-1*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-
 - 25 quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - Methyl 2-methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
 - 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,
 - 30 - Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoate,
 - 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-

quinazolin-3-ylmethyl]-benzoic acid,

- Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

5 - 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,

- 1-Methyl-2,4-dioxo-3-(pyridin-4-methyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide,

- 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide,

10 - 1-Methyl-2,4-dioxo-3-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-hydroxy-benzylamide,

- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

15 - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,

- Methyl 4-[1-methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

- 4-[1-Methyl-6-(4-methylsulfanyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,

20 - Methyl 4-[1-ethyl-2,4-dioxo-6-(4-trifluoromethoxy-benzylcarbamoyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

- Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

25 - 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,

- Methyl 4-{6-[(benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,

- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,

30 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,

- Methyl 4-[1-ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-

quinazolin-3-ylmethyl]-benzoate,

- 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,

- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Hydroxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 1-Methyl-2,4-dioxo-3-(3-pyridin-4-yl-allyl)-1,2,3,4-tetrahydro-quinazolin-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,

- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,

- Methyl (4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetate,

- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetic acid,

- Methyl 4-{1-methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,

- 4-{1-Methyl-2,4-dioxo-6-[(1-oxy-pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,

- Methyl {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-1-yl}-acetate,

- {6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-3-benzyl-2,4-dioxo-3,4-dihydro-2H-quinazolin-1-yl}-acetic acid,

- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,

- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid,

- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-6-carboxylic acid

- 4-sulfamoyl-benzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid [3-(pyridin-4-ylsulfany)-propyl]-amide,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
- 5 (4-morpholin-4-yl-butyl)-amide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1-benzyl-piperidin-4-yl)-amide,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
- 4-hydroxy-benzylamine,
- 10 - Ethyl (4-[[[(3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl]-phenoxy)-acetate,
- (4-[[[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)amino]-methyl]-phenoxy)-acetic acid,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
- 15 4-dimethylcarbamoylmethoxy-benzylamide,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (3-phenyl-allyl)-amide,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
- 4-cyano-benzylamide,
- 20 - 4-[[[(3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carbonyl)-amino]-methyl]-benzoic acid,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid
- 4-dimethylcarbamoyl-benzylamide,
- 3-(4-Dimethylamino-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic
- 25 acid 4-methoxy-benzylamide,
- 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - tert-Butyl {5-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-pyridin-2-yl}-carbamate,
- 30 - 3-(6-Amino-pyridin-3-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidine-6-carboxylic acid

- (1,3-benzodioxol-5-ylmethyl)-amide,
- 1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[2,3-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
 - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*] pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*] pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
 - Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoate,
 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
 - 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*] pyrimidin-3-ylmethyl]-benzoic acid,
 - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-*d*]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-Benzyl-1-methyl-6-(3-phenyl-propionyl)-1*H*-quinazoline-2,4-dione,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-4-yl-allyl ester,
 - 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (E)-3-pyridin-3-yl-allyl ester,
 - 3-Benzyl-1-methyl-6-[2-(pyridin-4-ylsulfanyl)-acetyl]-1*H*-quinazoline-2,4-dione,
 - 3-(4-Aminomethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 1-Methyl-2,4-dioxo-3-[2'-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,2,3,4-tetrahydro-

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- quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 4'-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylate,
 - 4'-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-biphenyl-2-carboxylic acid,
 - Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
 - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
 - 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester,
 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-2-methyl-benzoic acid 2-dimethylamino-ethyl ester,
 - 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-phenyl}-acetic acid,
 - 1-Methyl-3-(1-naphthalen-1-yl-ethyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
 - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
 - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
 - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
 - 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 3-methoxy-benzylamide,
 - 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
 - 1-Ethyl-3-(3-fluoro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic

acid (pyridin-3-ylmethyl)-amide,

- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,

- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,

- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,

- 3-(3-chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(3-Chloro-4-fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate(2-hydroxy-ethyl)-trimethyl-ammonium,

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemicalcium ,

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemimagnesium ,

- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,

- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide,

- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic

- acid 3-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 - 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
 - 5 - tert-Butyl 1-{4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylate,
 - 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid,
 - 10 - 3-Benzyl-6-benzylsulfanyl-1-methyl-1H-quinazoline-2,4-dione,
 - 3-Benzyl-1-methyl-6-phenylmethanesulfinyl-1H-quinazoline-2,4-dione,
 - 3-Benzyl-1-methyl-6-phenylmethanesulfonyl-1H-quinazoline-2,4-dione,
 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid tert-butoxycarbonylmethyl ester,
 - 15 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid dimethylamino-dimethyl-propyl ester,
 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid dimethylamino-methyl-propyl ester,
 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester,
 - 20 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid chloromethyl ester,
 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-tert-butoxycarbonylamino-3-methyl-1-butanoyloxymethyl ester,
 - 25 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-amino-3-methyl-butanoyloxymethyl ester hydrochloride,
 - 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-(2-tert-butoxycarbonylamino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester,
 - 30 - and 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazoline-3-ylmethyl]-benzoic acid 2-(2-amino-3-methyl-butanoylamino)-3-methyl-butanoyloxymethyl ester

16-A compound of formula (I) according to Claim 1 which is

- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid (1,3-benzodioxol-5-ylmethyl)-amide,
- 4-[6-(4-Fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- 1-Methyl-2,4-dioxo-3-[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-benzyl]-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid hemicalcium salt,
- Methyl 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoate,
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- 1-Methyl-2,4-dioxo-3-[4-(2H-tetrazol-5-yl)-benzyl]-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 2-hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoate,
- 3-(4-Chloro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid 3-methoxy-benzylamide,
- 4-{6-[(1,3-Benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl}-benzoic acid,
- 2-Hydroxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- Methyl 4-[6-(3-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoate,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 3-methoxy-benzylamide,
- 4-Pyridylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate,

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- Methyl 4-{6-[(1,3-benzodioxol-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,
- 1-Methyl-3-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 5 - 1-Methyl-3-[4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*]-
10 quinazolin-3-ylmethyl]-benzoic acid,
- 1-{4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-phenyl}-cyclopropanecarboxylic acid,
- 4-Pyridylmethyl 3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline -6-carboxylate,
- 15 - 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 3-methoxy-benzylamide,
- 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Dimethylcarbamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-
20 tetrahydroquinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-3-[4-(2-methyl-2*H*-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Bromo-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide,
- 25 - 3-(3,4-Difluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-3-ylmethyl)-amide,
- Benzo[1,3]dioxol-5-ylmethyl-3-benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
30 (benzo[1,3]dioxol-5-ylmethyl)amide,
- 1-Methyl-3-(4-methylcarbamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,

- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(4-Hydroxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 5 - Methyl 4-[6-(4-fluoro-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide ,
- 1-Methyl-3-[4-(1-methyl-1H-tetrazol-5-yl)-benzyl]-2,4-dioxo-1,2,3,4-
- 10 tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid 4-methoxybenzylamide,
- 4-Pyridylmethyl 3-(benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate,
- 15 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 1-Methyl-2,4-dioxo-3-pyridin-4-ylmethyl-1,2,3,4-tetrahydro-quinazoline-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Amino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
- 20 carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-3-(4-nitro-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 2-Methoxy-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 25 - 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 1-Methyl-2,4-dioxo-3-(4-sulfamoyl-benzyl)-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-
- 30 carboxylic acid 4-methoxy-benzylamide,
- 3-(4-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,

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- 3-(4-Methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 2-Methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- 5 - 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinoxalin-3-ylmethyl}-benzoic acid,
- 3-(3-fluoro-4-methoxy-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy benzylamine,
- 10 - 4-[1-Ethyl-6-(4-methoxy-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- 3-(Benzo[1,3]dioxol-5-ylmethyl)-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline -6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 15 - 3-(2'-Cyano-biphenyl-4-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[1-Methyl-6-(4-methylsulfonyl-benzylcarbamoyl)-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoic acid,
- 4-{6-[(Benzofurazan-5-ylmethyl)-carbamoyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl}-benzoic acid,
- 20 - Methyl 2-methyl-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-benzoate,
- 3-(4-Acetylamino-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- 25 - 3-(Benzo[1,3]dioxol-5-ylmethyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide,
- 3-(4-Dimethylcarbamoylmethyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinoxaline-6-carboxylic acid 4-methoxy-benzylamide,
- Benzo[1,3]dioxol-5-ylmethyl 3-benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylate,
- 30 - {4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-ylmethyl]-phenyl}-acetic acid,

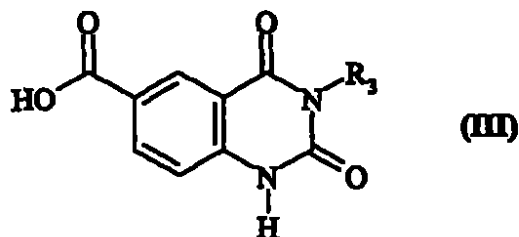
- (4-{1-Methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-phenyl)-acetic acid,
- 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
4-methoxybenzylamide,
- 5 - Methyl 4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-phenyl)-acetate,
- 3-(3-Fluoro-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid (pyridin-4-ylmethyl)-amide,
- 2,4-Dioxo-3-(thien-2-ylmethyl)-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid
10 (benzo[1,3]dioxol-5-ylmethyl)amide,
- 1-Methyl-3-(4-methylsulfamoyl-benzyl)-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Methyl 4-{1-methyl-2,4-dioxo-6-[(pyridin-4-ylmethyl)-carbamoyl]-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoate,
- 15 - 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid,
- 3-(4-Cyano-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[3,4-d]pyrimidine-6-carboxylic acid 4-methoxy-benzylamide,
- 4-[6-(3-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid,
- 20 - 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid hemmagnesium salt,
- 4-[6-(4-Methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[2,3-d]pyrimidin-3-ylmethyl]-benzoic acid,
- 25 - 3-[4-(N-methylsulfonylamino)-benzyl]-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- Ethyl 2-Fluoro-4-[6-(4-methoxy-benzylcarbamoyl)-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoate,
- 3-(4-Dimethylsulfamoyl-benzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-quinazoline-6-carboxylic acid 4-methoxy-benzylamide,
- 30 - and 3-(4-Methoxybenzyl)-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)amide.

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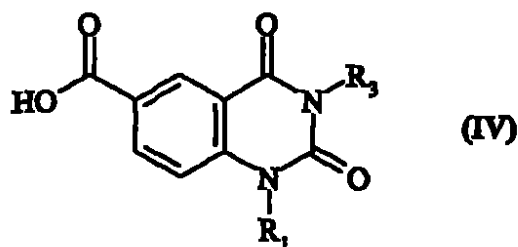
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17-Intermediate compound of formula (III)



in which R₃ is as defined in the compound of formula (I)

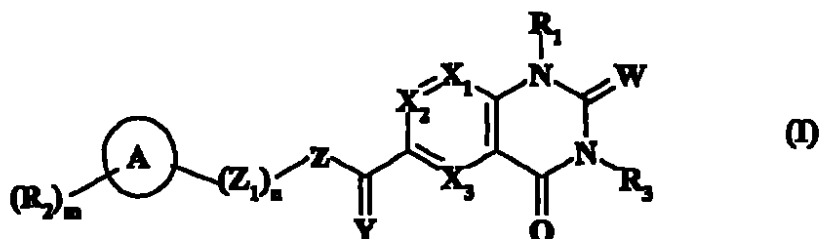
18-Intermediate compound of formula (IV)



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in which R₁ et R₃ are as defined in the compound of formula (I)

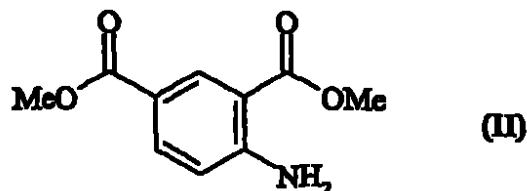
19- Process for manufacturing a compound of general formula (I)



10

in which R₂, R₃, Z₁, A, n and m are as defined in Claim 1, R₁ is H, X₁, X₂ and X₃ are CH, Y is O, Z is N-R₇ and W is O,

the said process being characterized in that it comprises the reaction of a compound of formula (II)



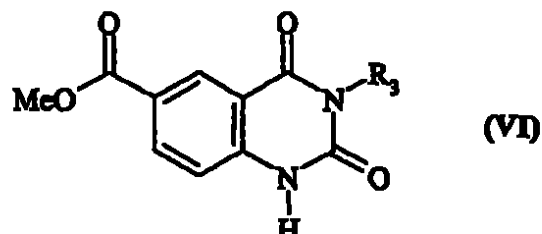
with pyridine and the compound of general formula (V)

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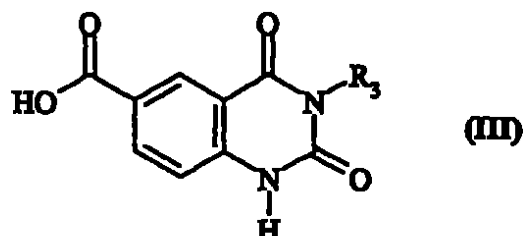
in which R_3 is as defined in Claim 1,

to give the compound of general formula (VI)

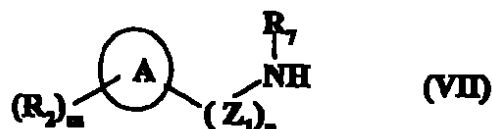


5 in which R_3 is as defined hereinbefore,

followed by reacting the compound of general formula (VI) in the presence of LiOH to give the compound of general formula (III) in which R_3 is as defined hereinbefore



10 the said compound of general formula (III) is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII)



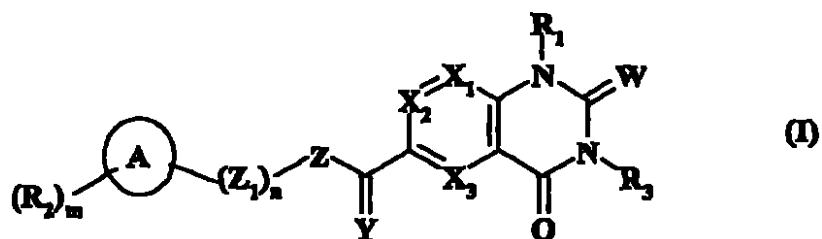
in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A , R_2 , Z_1 , m and n are as defined in Claim 1,

15 to give the compound of general formula (I) in which R_1 represents hydrogen, X_1 , X_2 and X_3 are CH , Y is O , Z is $\text{N}-\text{R}_7$, W is O , and A , R_2 , R_3 , Z_1 , m and n are as defined hereinbefore.

20- Process for manufacturing a compound of general formula (I)

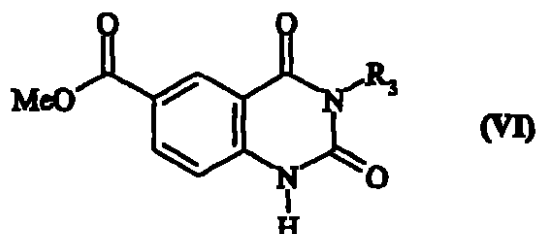
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in which R_1 , R_2 , R_3 , A , Z_1 , m and n are as defined in Claim 1, X_1 , X_2 and X_3 are CH, W is O, Y is O and Z is N- R_7 ,

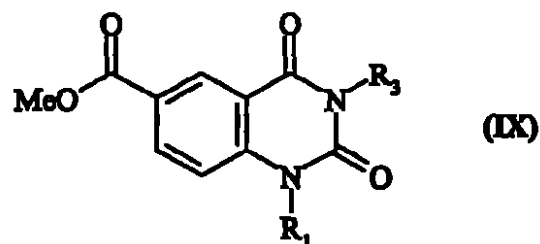
the said process being characterized in that a compound of general formula (VI)



5

in which R_3 is as defined in Claim 1,

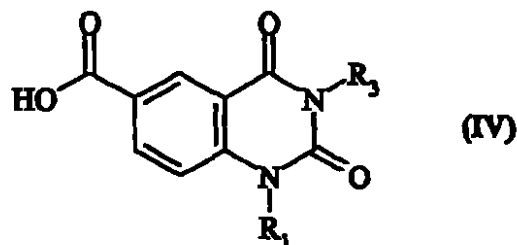
is reacted, in the presence of a base, with compound (VII) of general formula X- R_1 , in which R_1 is as defined in Claim 1 and X is a leaving group such as halogen, to give the compound of general formula (IX)



10

in which R_1 and R_3 are as defined hereinbefore,

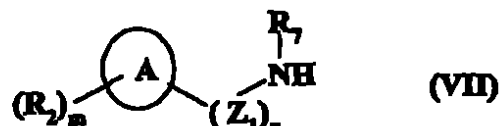
said compound of general formula (IX) is reacted in the presence of LiOH to give the compound of general formula (IV)



15

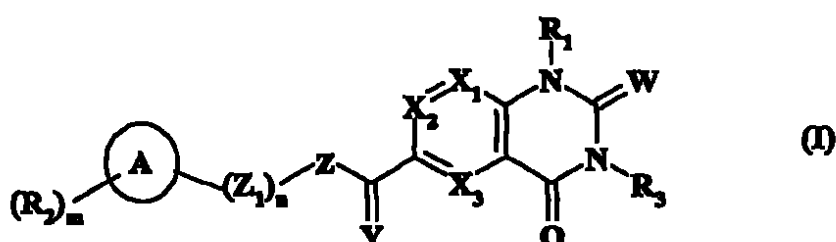
in which R_1 and R_3 are as defined hereinbefore,

said compound of general formula (IV) is reacted, in the presence of an acid activator such as TOTU, with the compound of general formula (VII)



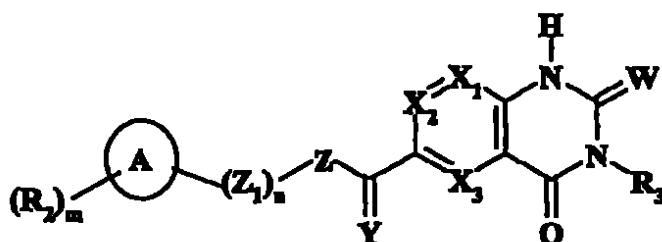
5 in which R_7 is selected from hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, aryl $(\text{C}_1\text{-C}_6)$ alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention,

to give the compound of general formula (I)



in which R_1 , R_2 , R_3 , A, Z_1 , m and n are as defined in the Claim 1, X_1 , X_2 and X_3 are CH, W is O, Y is O and Z is N- R_7

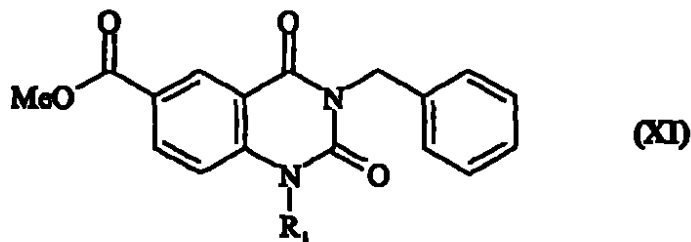
10 21- Process for manufacturing the compound of general formula (I) in which R_1 , R_2 , R_3 , W, X_1 , X_2 , X_3 , A, Z_1 , m and n are as defined in Claim 1, Y is O and Z is N- R_7 , characterized in that a compound of general formula (I)



15 in which R_1 is H, and R_2 , R_3 , W, Y, Z, X_1 , X_2 , X_3 , A, Z_1 , m and n are as defined hereinbefore,

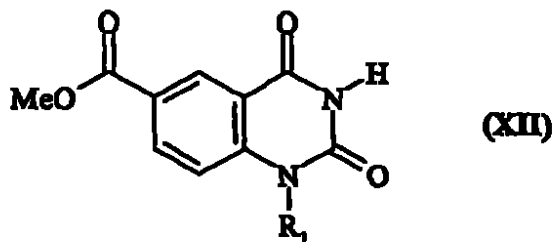
is reacted, in the presence of a base, with a compound (VIII) of general formula X-R_1 , in which R_1 is as defined in Claim 1 and X is a leaving group such as halogen, to give the compound of general formula (I) in which R_1 is as defined in Claim 1

22- Process for manufacturing a compound of general formula (I) in which X_1 , X_2 and X_3 are CH, W is O, Y is O, Z is N- R_7 , R_3 is H, and R_1 , R_2 , A, Z_1 , m and n are as defined in Claim 1 characterized in that a compound of general formula (XI)



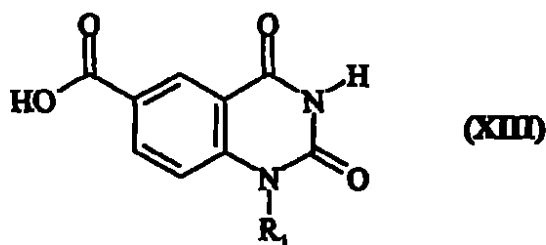
5 in which R_1 is as defined hereinbefore,

is reacted with $AlCl_3$ in a solvent such as benzene, to give the compound of general formula (XII)



in which R_1 is as defined hereinbefore,

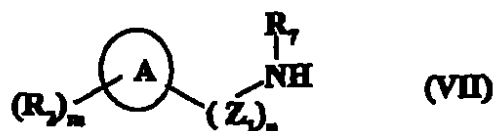
10 said compound of general formula (XII) is reacted in the presence of $LiOH$ and a mixture of dioxane/ H_2O to give the compound of general formula (XIII)



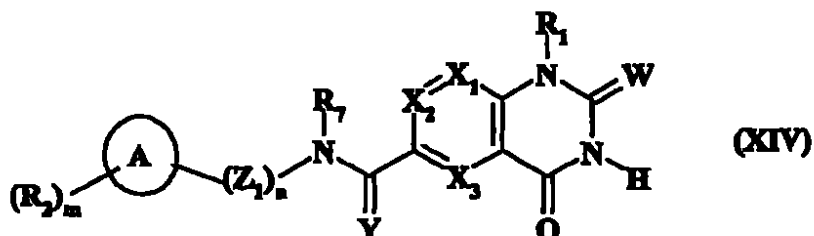
in which R_1 is as defined hereinbefore,

15 said compound of general formula (XIII) is reacted, in the presence of an acid activator such as TOTU with the compound of general formula (VII)

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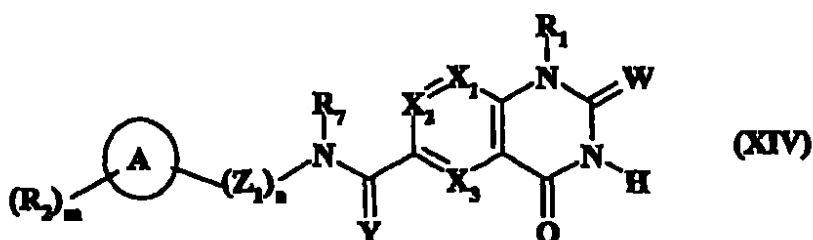
in which R_7 is selected from hydrogen, (C₁-C₆)alkyl, aryl(C₁-C₆)alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in Claim 1, to give the compound of general formula (XIV)



5

in which X_1 , X_2 and X_3 are CH, W is O, Y is O, and R_7 , A, R_2 , R_1 , Z_1 , m and n are as defined hereinbefore

23-The process for manufacturing a compound of general formula (I) characterized in that it comprises a step in which the compound of general formula (XIV)



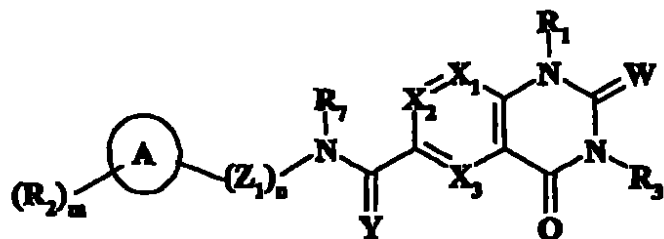
10

in which X_1 , X_2 and X_3 are CH, W is O, Y is O, and R_7 , A, R_2 , R_1 , Z_1 , m and n are as defined in Claim 1,

is reacted with compound (XV) of general formula $X-R_3$, in which R_3 is as defined in Claim 1 and X is a leaving group such as halogen,

15

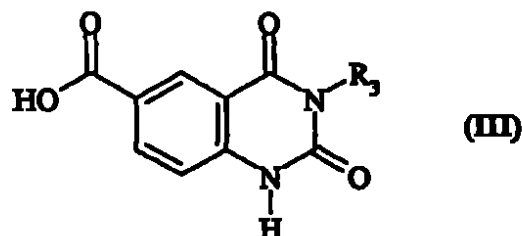
to give the compound of general formula (I)



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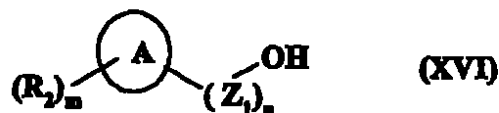
in which X_1 , X_2 and X_3 are CH, W is O, Y is O, and R_7 , A, R_2 , R_3 , R_1 , Z_1 , m and n are as defined in Claim 1,

5 24- Process for manufacturing a compound of general formula (I) in which X_1 , X_2 and X_3 are CH, W is O, Y is O and Z is O, characterized in that a compound of general formula (III)



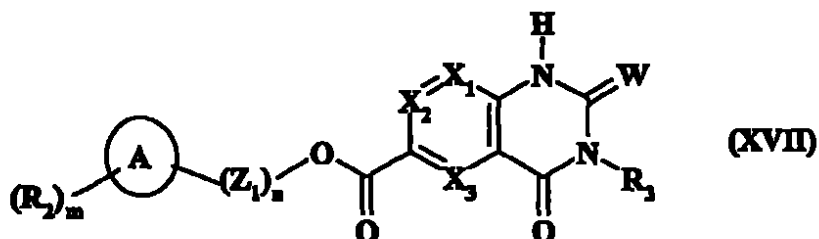
in which R_3 is as defined in Claim 1,

is reacted with a compound of general formula (XVI)



10 in which A, R_2 , Z_1 , m and n are as defined in Claim 1,

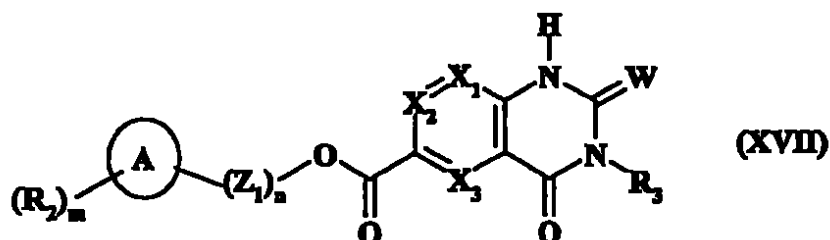
to give a compound of general formula (XVII)



in which A, R_2 , R_3 , Z_1 , m and n are as defined hereinbefore, X_1 , X_2 and X_3 are CH, and W is O

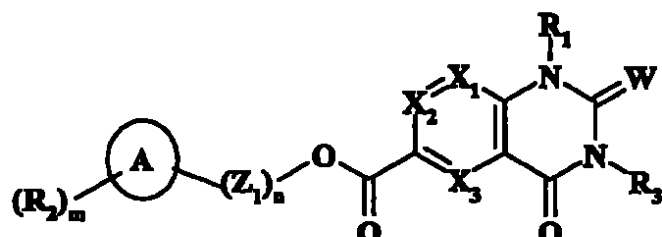
15 25- Process for manufacturing a compound of general formula (I), the said process is characterized in that the compound of formula (XVII)

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in which A, R₂, R₃, Z₁, m and n are as defined in Claim 1, X₁, X₂ and X₃ are CH, and W is O,

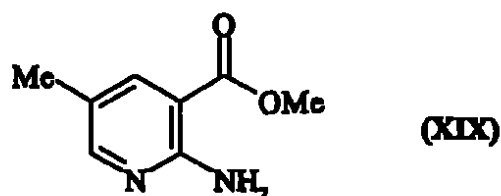
is reacted, in the presence of a base, with compound (VIII) of general formula X-R₁, in which R₁ is as defined in Claim 1 and X is a leaving group such as halogen, to give the compound of general formula (I)



in which A, R₁, R₂, R₃, Z₁, m and n are as defined in hereinafore, X₁, X₂ and X₃ are CH, and W is O

26- Process for manufacturing a compound of general formula (I) in which X₂ and X₃ are CH, X₁ is N, Z is O, Y is O, R₁ is H, W is O, and A, R₂, R₃, Z₁, m and n are as defined in Claim 1,

characterized in that the said process comprises a step in which a compound of general formula (XIX)

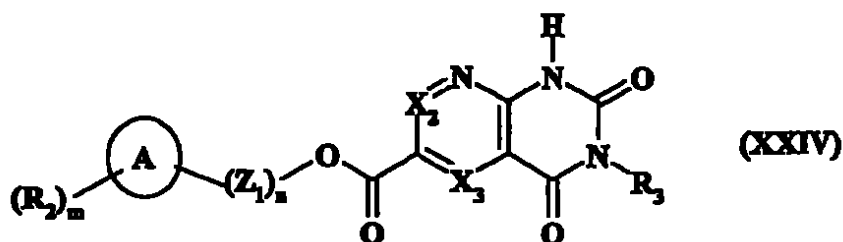


is reacted with pyridine and a compound (V) of general formula O=C=N-R₃ in which R₃ is as defined in Claim 1,

to give a compound of general formula (XX)

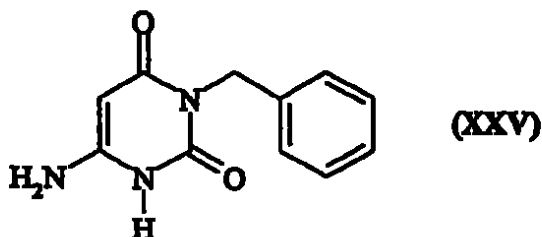
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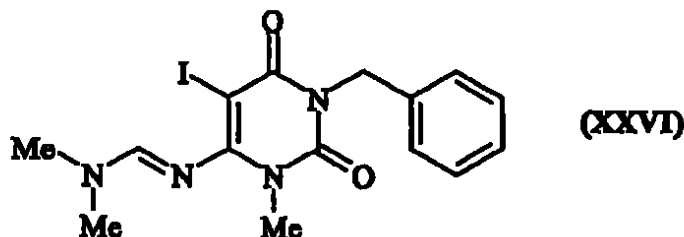


in which X_2 and X_3 are CH and A, n, m, Z_1 , R_2 and R_3 are as defined hereinbefore.

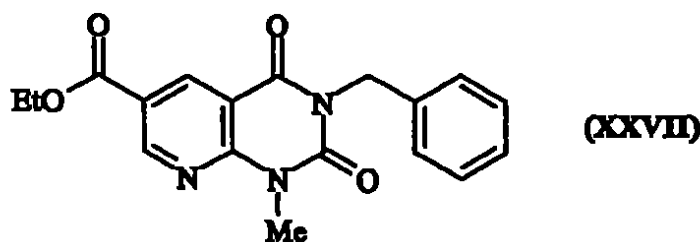
- 27- A process for manufacturing a compound of general formula (I) in which X_2 and X_3 are CH, X_1 is N, Z is $-NR_7$ in which R_7 is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXV)



- is reacted in a first step with N,N'-dimethylformamide dimethyl acetal under reflux of DMF, and in a second step with N-iodosuccinimide, to give a compound of formula (XXVI)

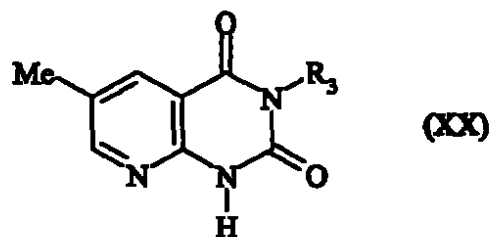


followed by reacting the compound of formula (XXVI) with ethyl acrylate in the presence of palladium diacetate, CuI and a base, to give the compound of general formula (XXVII)



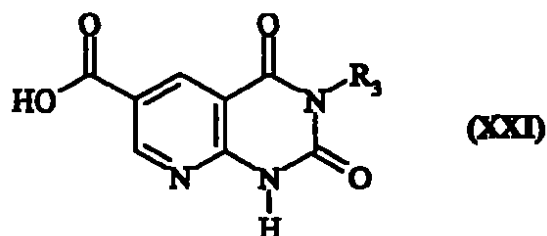
- 15 followed by reacting the compound of formula (XXVII) in the presence of LiOH to give the compound of general formula (XXVIII)

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in which R₃ is as defined hereinbefore,

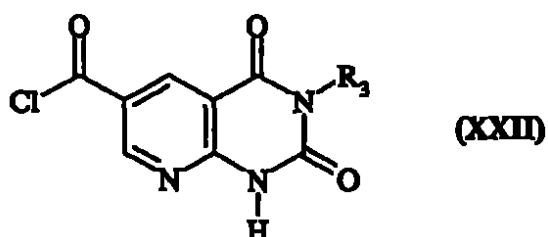
said compound of general formula (XX) is reacted in the presence of KMnO₄ to give the compound of general formula (XXI)



5

in which R₃ is as defined hereinbefore,

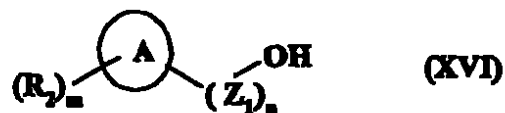
said compound of general formula (XXI) is reacted in the presence of SOCl₂ and optionally of a solvent to give the compound of general formula (XXII)



10

in which R₃ is as defined hereinbefore,

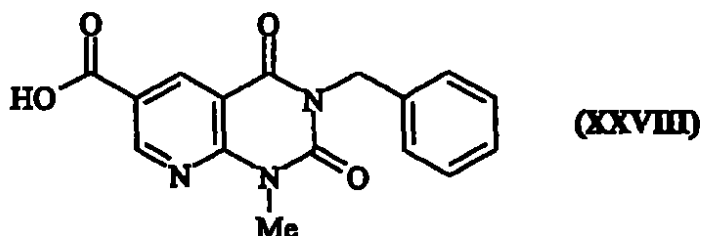
said compound of formula (XXII) is reacted with the compound of general formula (XVI)



in which A, R₂, Z₁, n and m are as defined in Claim 1,
to give the compound of general formula (XXIV)

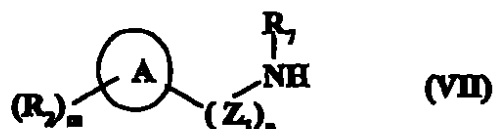
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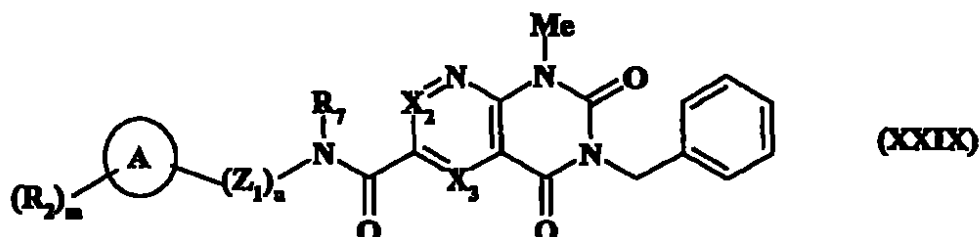


the said compound of formula (XXVIII)

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII)

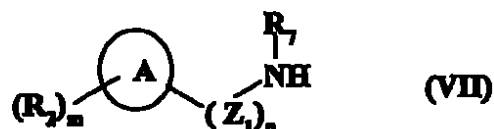


in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXIX)



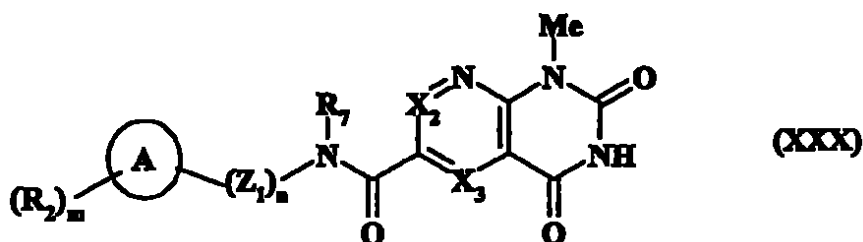
- in which A, R_2 , R_7 , Z_1 , m and n are as defined hereinbefore, and X_2 and X_3 represents each -CH group,

- or is reacted in a first step with $AlCl_3$ in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII)



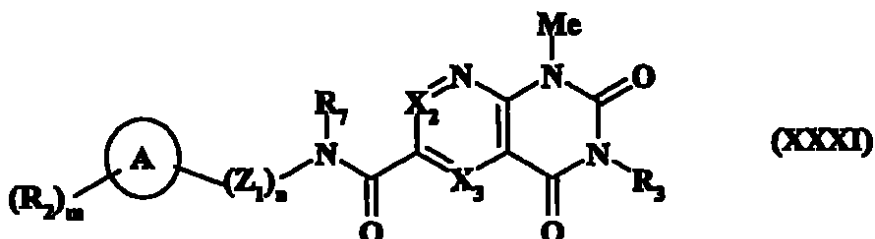
- in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A, R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXX)

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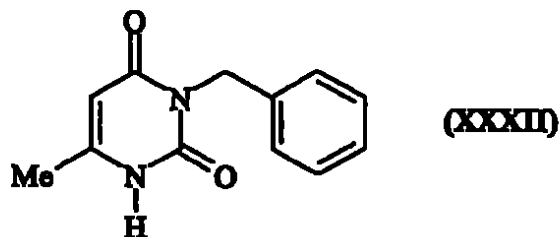
in which A, R₂, R₇, Z₁, m and n are as defined hereinbefore, and X₂ and X₃ represents each -CH group,

5 followed by reacting the compound of formula (XXX) with a compound of formula R₃-X in which R₃ is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXI)



28- A process for manufacturing a compound of general formula (I) in which X₁ and X₃ are CH, X₂ is N, Z is -NR₇ in which R₇ is as defined in the compound of formula (I), W is O, and Y is O, characterized in that the said process comprises a step in which a compound of general (XXXII)

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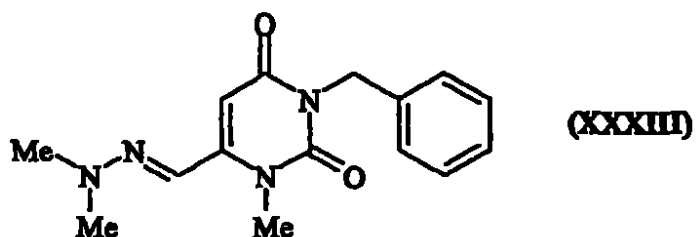


is reacted in a first step with selenium dioxide in the presence of acetic acid, in a second step with dimethylhydrazine, and in a third step with N,N'-dimethylformamide dimethylacetal under reflux of DMF, to give a compound of formula (XXXIII)

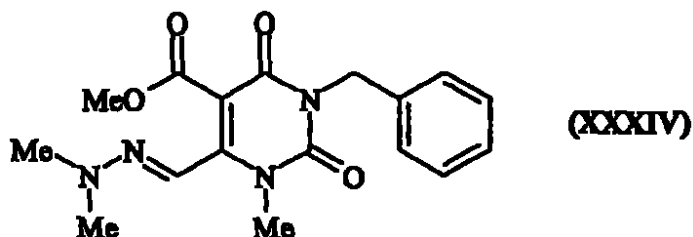
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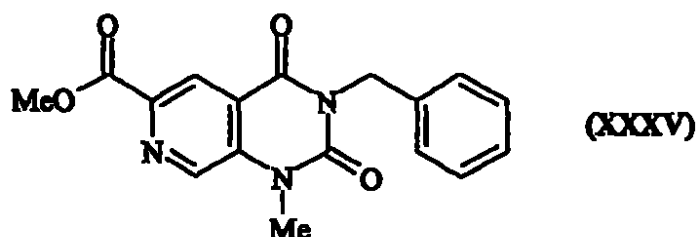
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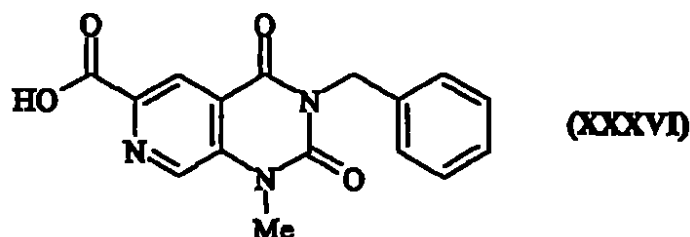
followed by reacting the compound of formula (XXXIII) with methyl acrylate in the presence of palladium diacetate, to give the compound of general formula (XXXIV)



- 5 followed by reacting the compound of formula (XXXIV) with chlorobenzene and acetic acid to give the compound of formula (XXXV)



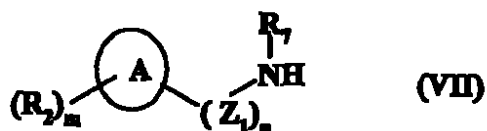
followed by reacting the compound of formula (XXXV) in the presence of a base to give the compound of general formula (XXXVI)



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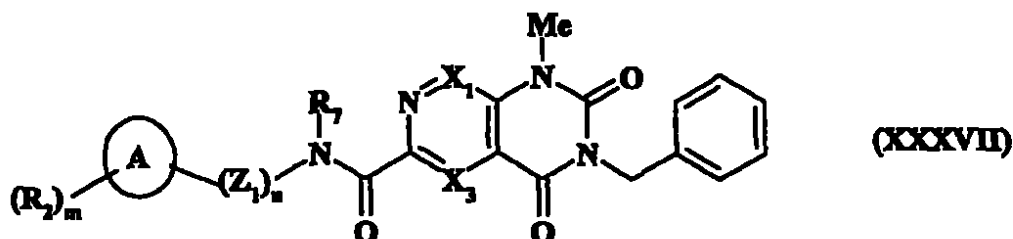
the said compound of formula (XXXVI)

- either is reacted, in the presence of an acid activator such as TOTU, with the compound of formula (VII)



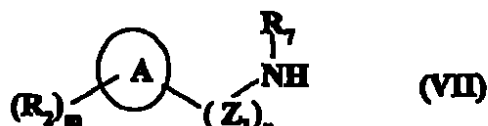
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in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A , R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVII)

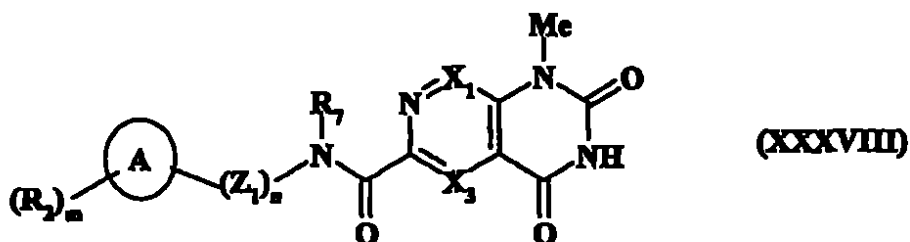


5 in which A , R_2 , R_7 , Z_1 , m and n are as defined hereinbefore, and X_1 and X_3 represents each $-CH$ group,

- or is reacted in a first step with $AlCl_3$ in the presence of benzene, and in a second step in the presence of an acid activator such as TOTU, with the compound of formula (VII)



10 in which R_7 is selected from hydrogen, (C_1-C_6) alkyl, aryl (C_1-C_6) alkyl, cycloalkyl, aryl and heteroaryl, and A , R_2 , Z_1 , m and n are as defined in the summary of the invention, to give the compound of general formula (XXXVIII)

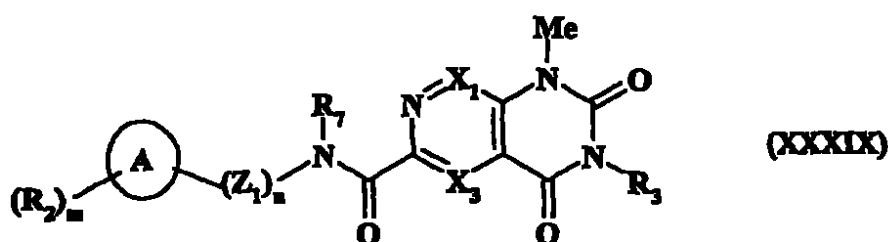


15 in which A , R_2 , R_7 , Z_1 , m and n are as defined hereinbefore, and X_1 and X_3 represents each $-CH$ group,

followed by reacting the compound of formula (XXXVIII) with a compound of formula R_3-X in which R_3 is as defined in the compound of general formula (I), in the presence of a base, to give the compound of formula (XXXIX)

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29- Pharmaceutical composition comprising a compound according to any one of Claims 1 to 15 and a pharmaceutically acceptable excipient.

30- Use of a compound according to any one of Claims 1 to 16, for the preparation of a medicinal product intended for treating a disease or complaint involving therapy by inhibition of type-13 matrix metalloprotease.

31- Use according to Claim 30, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers.

32- Use according to Claim 31, characterized in that the disease is arthritis

33- Use according to Claim 31, characterized in that the disease is osteoarthritis

34- Use according to Claim 31, characterized in that the disease is rheumatoid arthritis

35- A method for treating a disease or complaint involving a therapy by inhibition of MMP-13, the said method comprising the administration of an effective amount of a compound according to any one of Claims 1 to 16 to a patient

36- A method for treating according to Claim 35 characterized in that the disease or the complaint are selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis,

periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease (COPD), age-related macular degeneration (ARMD) and cancers

5 37- A method for treating according to Claim 35 characterized in that the disease is arthritis

38- A method for treating according to Claim 35 characterized in that the disease is osteoarthritis

39- A method for treating according to Claim 40 characterized in that the disease is rheumatoid arthritis

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INTERNATIONAL SEARCH REPORT

In Application No
PCT/EP 02/01979

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D239/96	C07D401/12	C07D405/12	C07D409/12	C07D405/14
	C07D409/14	C07D471/04	C07D403/12	C07D403/10	C07D401/10
	C07D413/10	C07D401/06	A61K31/5025	A61K31/505	

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

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

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

WPI Data, PAJ, BEILSTEIN Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIVERTON N J ET AL "Nonpeptide glycoprotein IIb/IIIa inhibitors substituted quinazolinones and quinazolinones as potent fibrinogen receptor antagonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol 8, no 5, 3 March 1998 (1998-03-03), pages 483-486, XP004136889 ISSN 0960-894X see compound 7 page 481	17,18
X	H OGAWA ET AL "Studies on positive inotropic agents V" CHEM PHARM BULL, vol 36, no 6, 1988, pages 2253-2258, XP001080174 see compound X chart I	17,18
-/-		

☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

* Special categories of cited documents A document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (see 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. A document member of the same patent family	
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Date of the actual completion of the international search	Date of mailing of the international search report
4 June 2002	25/06/2002

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentplan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2340, Tx. 31 651 epo nl, Fax (+31-70) 340-2018	Authorized officer Scruton-Evans, I
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INTERNATIONAL SEARCH REPORT

 Int. Application No.
 PCT/EP 02/01979

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 ³/(C07D471/04, 239 00, 221 00)

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)

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201020 ORDER NO A1240/0056923 & "SCREENING COLLECTION" 28 March 2000 (2000-03-28), ZELINSKY INSTITUTE OF ORGANIC CHEMISTRY, 47 LENINSKY PROSPECT, MOSCOW, 117913 RUSSIA — -/-	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents

- A document defining the general state of the art which is not considered to be of particular relevance
- E⁺ earlier document but published on or after the international filing date
- T⁺ 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 relating 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.
- A document member of the same patent family

Date of the actual completion of the international search

4 June 2002

Date of mailing of the international search report

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 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-2010

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X,P	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201021 ORDER NOS CHS 1938401 CHS 1938397 CHS 1938395 & "CHEMSTAR PRODUCT LIST" 16 May 2001 (2001-05-16), CHEMSTAR LTD, LENINGRADSKII PROSPECT 47, OFFICE 465, MOSCOW, 125167 RUSSIA	1
P,X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201022 ORDER NOS STOCKIN-2756, A1336/0060317, STOCKIS-85693, STOCKIS-77305, STOCKIS-81043, STOCKIS-82046 & "AMBINTER EXPLORATORY LIBRARY" 21 January 2002 (2002-01-21), AMBINTER, 46 QUAI LOUIS BLERiot, PARIS, F-75016, FRANCE	1
P,X	DATABASE CHEMCATS 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, XP002201023 ORDER NOS C-055658, C-055656, Z-007159, Z-007158, C-055659 & "SCIENTIFIC EXCHANGE PRODUCT LIST" 1 June 2001 (2001-06-01), SCIENTIFIC EXCHANGE, INC, PINE RIVER ROAD, PO BOX 918, CENTER OSSIPPEE, NH 03814, USA	1
X	CHEMICAL ABSTRACTS, vol 54, no 3, 10 February 1960 (1960-02-10) Columbus, Ohio, US, abstract no 2375e, NESTEROV XP002201019 abstract & SU 119 879 A (NESTEROV ET AL) 21 May 1959 (1959-05-21) Compound pyrimido'5,4-d'pyrimidine-2,4(1H,3H)-dione, 6-(benzylthio)-, RN 100382-60-3 -/-	1

INTERNATIONAL SEARCH REPORT

 Int. Application No.
 PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, MURATA, SHIZUAKI ET AL "Regioselective synthesis of 6-substituted lumazines by using highly reactive lumazine 6-triflate" retrieved from STN Database accession no 128 243870 XP002201024 abstract & CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 17-22 EDITOR(S) PFLEIDERER, WOLFGANG ROKOS, HARTMUT PUBLISHER BLACK, compound RN 191275-58-8	1
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, KIM, YEONHEE ET AL "Side chain reactions of 6-acetyl-1,3,7-trimethylumazine" retrieved from STN Database accession no 128 243871 XP002201025 abstract & CHEMISTRY AND BIOLOGY OF PTERIDINES AND FOLATES 1997, PROCEEDINGS OF THE INTERNATIONAL SYMPOSIUM ON PTERIDINES AND FOLATES, 11TH, BERCHTESGADEN, GERMANY, JUNE 15-20, 1997 (1997), 41-44 EDITOR(S) PFLEIDERER, WOLFGANG ROKOS, HARTMUT PUBLISHER BLACK, compound RN 109879-41-6	1
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, ABOU-HADEED, KHALED ET AL "Pteridines CVIII Reactions of 6,7-dichloro-1,3-dimethylumazine with sulfur nucleophiles" retrieved from STN Database accession no 126 212115 XP002201026 compound RN 188023-01-0 abstract & PTERIDINES (1996), 7(4), 113-122 , — -/-	1

INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, SLADOWSKA, H ET AL "Synthesis and properties of amides of 1-benzyl-3-methyl- and 1-butyl-3-phenyl-7-methyl-4-oxo-2-thioxo (2,4-dioxo)-1,2,3,4-tetrahydropyrido'2,3-d'pyrimidine-6-carboxylic acids" retrieved from STN Database accession no 107 58977 XP002201027 compounds 109493-30-3 and 109493-25-6 abstract & FARMACO, ED SCI (1986), 41(12), 954-63	1,29
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, LESPAGNOL, ALBERT ET AL "Study on antifolic agents 1 Derivatives of 4-nitrobenzene-1,3- dicarboxylic acid" retrieved from STN Database accession no 87 152121 XP002201028 compound RN 64152-16-5 abstract & BULL SOC PHARM LILLE (1977), 33(1), 67-77	1
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US, GHOSE, ARUP K ET AL "A general distance-geometry three-dimensional receptor model for diverse dihydrofolate reductase inhibitors" retrieved from STN Database accession no 101 16805 XP002201029 compound RN 52979-05-2 and 52979-04-1 abstract & J MED CHEM (1984), 27(7), 901-14	1,29
X	DE 24 41 959 A (CIBA GEIGY AG) 13 March 1975 (1975-03-13) compound rn 56044-13-4, Piperidine,1- '(1,2,3,4-tetrahydro-2,4-dioxo-6-quinazolinyl)sulfonyl'	1

INTERNATIONAL SEARCH REPORT

 b
 of Application No
 PCT/EP 02/01979

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 64400 A (BEMIS GUY , VERTEX PHARMA (US), COCHRAN JOHN (US), SALITURO FRANCES) 16 December 1999 (1999-12-16) see general formula and page 5, lines 17-end	1-39
A	REITER L A ET AL "Inhibition of MMP-1 and MMP-13 with phosphinic acids that exploit binding in the S2 pocket" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol 9, no 2, 18 January 1999 (1999-01-18), pages 127-132, XP004152585 ISSN 0960-894X the whole document	1-39
A	CHEN J M ET AL "STRUCTURE-BASED DESIGN OF A NOVEL, POTENT, AND SELECTIVE INHIBITOR FOR MMP-13 UTILIZING NMR SPECTROSCOPY AND COMPUTER-AIDED MOLECULAR DESIGN" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol 122, 2000, pages 9648-9654, XP001010185 ISSN 0002-7863 the whole document	1-39
A	WO 97 43239 A (BRITTELLI DAVID R , ZANDT MICHAEL C VAN (US), DIXON BRIAN R (US), B) 20 November 1997 (1997-11-20) the whole document	1-39

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INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 02/01979

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

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

- 1 ☒ Claims Nos. because they relate to subject matter not required to be searched by this Authority namely
Although claims 35-39 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

In **International Application No**
PCT/EP 02/01979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
SU 119879	A	NONE	
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		JP 11510821 T	21-09-1999
		WO 9743239 A1	20-11-1997
		ZA 9704030 A	19-02-1998

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(12) SOLICITUD INTERNACIONAL PUBLICADA DE ACUERDO CON EL
TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) ORGANIZACIÓN MUNDIAL DE LA PROPIEDAD INTELECTUAL

Oficina Internacional

5

PCT

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(22 08 2002)

(10) Publicación Internacional Número WO 02/064572 A1

(51) Clasificación Internacional de Patentes⁷

10 C07D 239/96, 401/12, 405/12, 409/12, 405/14, 409/14, 471/04,
403/12, 403/10, 410/10, 413/10, 401/06, A61K 31/5025, 31/505

(21) Solicitud Internacional Número PCT/EP02/01979

(22) Fecha de Presentación Internacional 11 de febrero de
2002 (11 02 2002)

15 (25) Idioma de la presentación inglés

(26) Idioma de la Publicacion inglés

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(74) **Agentes HIRSCH, Denise et al** , Pfizer Global Research and Development, Fresnes Laboratories, 3-9, rue de la Loge, B P 100, F-97265 Fresnes Cedex (FR)

(81) **Estados Designados** (nacionales) 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

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(84) Estados Designados (regionales) Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, UG, ZM, ZW), Patente de Eurasia (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaraciones conforme a la Norma 4 17

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EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,
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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,
5 YU, ZA, ZM, ZW, Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL,
SZ, TZ, UG, ZM, ZW), Patente de Eurasia (AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB,

[continua en la página siguiente]

10 (54) Título QUINAZOLINAS COMO INHIBIDORES DE MMP-13

(57) Resumen de la invención Un compuesto seleccionado de aquellos de fórmula (I) donde

R₁ representa un grupo seleccionado de hidrógeno, amino,
15 alquilo, alquenilo, aminoalquilo, arilo, arilalquilo,
heterociclo, y cicloalquiloalquilo, sustituidos de manera
opcional, W representa oxígeno, azufre, o =N-R', donde R' es
como se lo define en la memoria descriptiva, X₁, X₂ y X₃
representan nitrógeno o -C-R₆ donde R₆ es como se lo define en
20 la memoria descriptiva, Y representa oxígeno, azufre, -NH, o -
N(C₁-C₆)alquilo, Z representa oxígeno, azufre, -NR₇ donde R₇ es
como se lo define en la memoria descriptiva, y de manera
opcional, átomo de carbono, n es un entero entre 1 y 8
inclusive, Z₁ representa -CR₈R₉ donde R₈ y R₉ son como se los
25 define en la memoria descriptiva, A representa un sistema de

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anillos aromáticos o no aromáticos, heterocíclicos o no heterocíclicos, m es un entero de 0 a 7 inclusive, el/los grupo(s) R_2 es/son como se los(s) define en la memoria descriptiva, R_3 representa hidrógeno, alquilo, alquenilo, alquinilo, o un grupo de fórmula $Z_2B(R_5)_P(R_6)_Q$ donde Z_2 , B , R_5 , P y Q son como se los define en la memoria descriptiva, de manera opcional, las formas racémicas de los mismos, isómeros de los mismos, N-óxidos de los mismos, y las sales farmacéuticamente aceptables de los mismos, y los productos medicinales que contienen lo mismo son de utilidad como inhibidores específicos de la metaloproteasa de matriz de tipo 13

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PÁGINA 2

GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

5 - de inventor (Norma 4 17(iv) para US solamente

Publicada

- con informe de búsqueda internacional
- con anterioridad al vencimiento del plazo establecido para
- 10 enmendar las reivindicaciones y para ser publicada nuevamente
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15 al comienzo de cada edición periódica del Boletín del PCT