05-118410.

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21 **EXPEDIENTE No** 05-118410

54 **TITULO** DERIVADOS DE PIRAZOLO-QUINAZOLINA, PROCESO PARA SU PREPARACION Y USO COMO INHIBIDORES DE QUINASA

51 **CLASIFICACION INTERNACIONAL** C07D 487/04

71 **SOLICITANTE** PHARMACIA ITALIA S p A

DOMICILIO MILAN, ITALIA

74 **APODERADO** ALVARO CORREA ORDOÑEZ
TP 20281

22 **BOGOTA, D C,** NOVIEMBRE 22 DE 2005

(FORMA P-10)

PETITORIO

000001

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05118418 00000000 Folios: 650
Fecha (AMD): 2005-11-22 16:57:52
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Radicación

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 22-Dic-2005

(1) SOLICITUD DE :

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I.	[X]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: PHARMACIA ITALIA S.p.A.

Dirección: Via Robert Koch 1.2, I-20152 Milán, Italia

Nacionalidad o Domicilio: ITALIANA
Lugar de Constitución: Milán, Italia

Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección Avenida 82 No.10-62 Piso 6o.

Teléfono: 634 1500 Fax 376 2211
E-Mail: patents.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.143.366 de Usaquén TP 20.281

(4) INVENTOR (ES) (72)

Nombre: TRAQUANDI, Gabriella; BRASCA, Maria Gabriella; D'ALESSIO, Roberto; POLUCCI, Paolo; ROLETTO, Fulvia; VULPETTI, Anna; PEVARELLO, Paolo; PANZERI, Achille; QUARTIERI, Francesca; FERGUSON, Ron; VIANELLO, Paola; y FANCELLI, Daniele.

Dirección: Via F.Clea, 106 I-20151 Milán, Italia; Via Dante Alighieri, 15 I-20090 Cusago (Milán) Italia; Via S.Paolo, 5 I-20092 Cinisello Balsamo (Milán) Italia; Via F. Sforza, 52, I-62100 Macerata, Italia; Via del Roccolo, 49 I-20020 Busto Garolfo (Milán) Italia; Via Volturno 80, Portici 3, I-20047 Brugherio (Milán) Italia; Piazza San Pietro in Ciel d'Oro, 7/a I-27100 Pavia, Italia; Via G. Matteotti, 8 I-23807 Merate (LC) Italia; Via Torino, 14 I-28041 Arona (NO) Italia; Via G. Verdi, 25 I-20120 Casale Litta (VA) Italia; Via Trebazio, 6 I-20145 Milán, Italia y Via Montecuccoli, 8 I-20147 Milán, Italia.

Nacionalidad o Domicilio: Italiana; Italiana; Italiano; Italiano; Italiana; Italiana; Italiano; Italiana; Italiana; Estadounidense; Italiana e Italiana.

(5) PCT (85)

Solicitud Internacional No. PCT/EP2004/050612 Fecha Abril 27, 2004
Publicación Internacional No. WO 2004/104007 A1 Fecha Diciembre 2, 2004

(6) Título (54) DERIVADOS DE PIRAZOLO-QUINAZOLINA, PROCESO PARA SU PREPARACIÓN Y SU USO COMO INHIBIDORES DE QUINASA.

(7) Clasificación Internacional (51) C07D 487/04

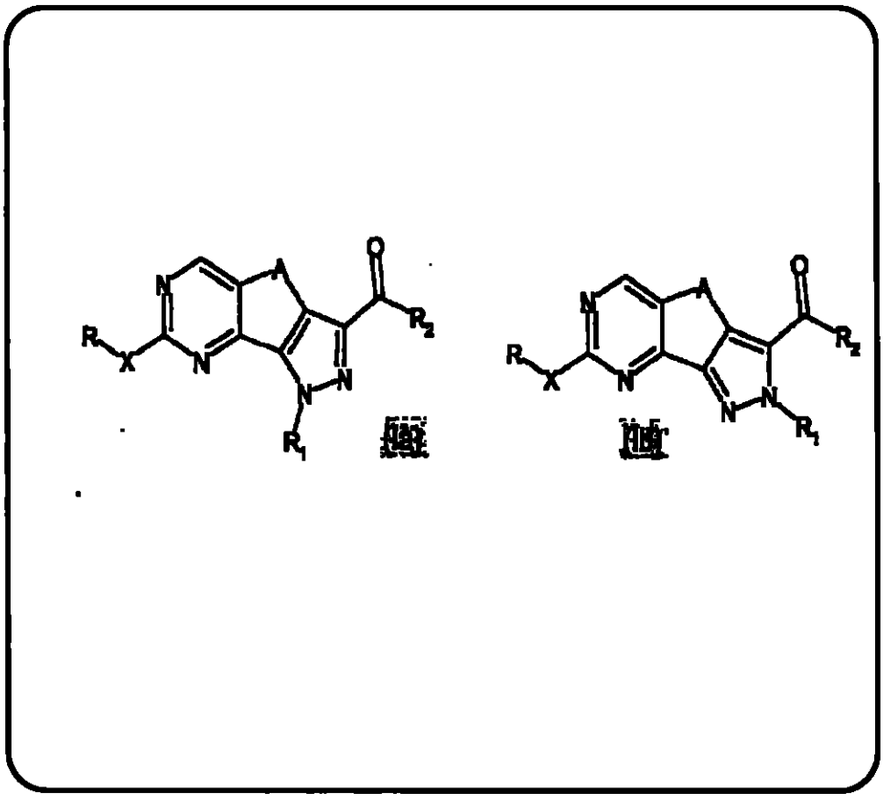
(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	Mayo 22, 2003	60/472,661

(9) Comprobante de pago No. 05-32,460 **Fecha** MAYO 4 DE 2005

(10) **ANEXOS** 000002

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

(11) **FIGURA CARATERISTICA**



(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

Instrucciones para la presentación de los anexos, ver reverso de esta página

SUPERINDUSTRIA Y COMERCIO

Radicacion : 05118418 00000000 Folios: 650
Fecha (AMD): 2005-11-22 16:57:52
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 05 - 32,460
FECHA : MAYO 4 DE 2005

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
ALVARO CORREA ORDOÑEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	37739480	04/05/2005	96,012,000.

C O N C E P T O

CANT.	NEMOTECNICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		443,000.00
		TOTAL :	$	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL No. 078/05 de un documento escrito en Inglés, el cual para su identificación se sella con el sello del Traductor. Esta es una Traducción Oficial efectuada el día 17 de febrero de 2005 por la Sra. María Teresa Lara, c.c. 41.568.055 de Bogotá, Traductora Oficial según Resolución No. 01016 del 2 de octubre de 1998, expedida por el Ministerio de Justicia.

= =

Poder otorgado por PHARMACIA ITALIA S.p.A. para su representación en relación con asuntos de propiedad industrial en Colombia. Certificación notarial suscrita por Jane E. Callahan, Notario Público del estado de Nueva York, EE.UU., y legalizaciones subsiguientes.

EL PODER NO SE TRADUCE POR ENCONTRARSE EN INGLÉS Y ESPAÑOL EN EL DOCUMENTO ORIGINAL.

MARIA TERESA LARA L.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINJUSTICIA

PODER GENERAL

Otorgado a Grover F. Fuller Jr.

con dirección Pfizer Inc.
150 East 42nd Street
New York, NY 10017-5612
E.U.A.

o a quien él pueda designar, para actuar en su nombre como nuestro representante en todos los países, en asuntos relacionados con solicitudes de patentes o diseños o en relación con la protección otorgada, con autoridad para suscribir cartas y documentos respecto de estos asuntos a nombre de la firma PHARMACIA & UPJOHN SpA.

Este poder podrá ser revocado en cualquier momento mediante un

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
22 NOV 2005
BOGOTA, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE

Instrumento escrito firmado por un funcionario debidamente autorizado de PHARMACIA & UPJOHN SpA.

Fecha 02/25/04

(Fdo.) Emanuele Barié

Presidente

LA CERTIFICACIÓN NOTARIAL NO SE TRADUCE POR ENCONTRARSE EN INGLÉS Y ESPAÑOL EN EL DOCUMENTO ORIGINAL.

[Sello notarial] JANE E. CALLAHAN
Notario Público, Estado de Nueva York
No. 01CA4959877
Habilitada en el Condado de Nueva York
La comisión expira 12/11/2005

Estado de Nueva York)
) ss.: No. 389290
Condado de Nueva York)

Yo, NORMAN GOODMAN, Secretario del Condado y Secretario del Tribunal Supremo del Estado de Nueva York, en y para el Condado de Nueva York, un Tribunal de Registro, legalmente provisto de sello,

CERTIFICO POR EL PRESENTE, de conformidad con la Ley Ejecutiva del Estado de Nueva York, que

Jane E. Callahan

COTEJADO CON EL ORIGINAL QUE SE HE TENIDO A LA VISTA
22 NOV 2005
BOGOTÁ, D.C. - COLOMBIA
ZOILA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

cuyo nombre suscribe el testimonio, declaración, certificado de reconocimiento o prueba adjunto, era en el momento de recibir el mismo una NOTARIO PUBLICO en y para el Estado de Nueva York, debidamente comisionada, juramentada y calificada para actuar como tal; que conforme a la ley, una comisión o un certificado de su carácter oficial, con su firma autógrafa, ha sido registrado en mi oficina; que en el momento de recibir dicha prueba, reconocimiento o juramento estaba debidamente autorizada para ello; que conozco bien la letra manuscrita de dicha NOTARIO PUBLICO o he comparado la firma que aparece en el instrumento adjunto con su firma autógrafa depositada en mi oficina y considero que dicha firma es auténtica.

EN FE DE LO CUAL, he firmado el presente y estampado mi sello oficial a los 27 días del mes de julio de 2004.

(Firmado) Norman Goodman

Secretario del Condado y Secretario del
Tribunal Supremo, Condado de Nueva York

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. País: **Estados Unidos de América**
   Este documento público
2. ha sido firmado por **Norman Goodman**
3. actuando en calidad de **Secretario del Condado**
4. lleva el sello/timbre del condado de **Nueva York**

22 NOV 2005

BOGOTÁ, D.C. - COLOMBIA
NOTARIA ONCE (11)

Certificado

5. en Nueva York, Nueva York 6. el día 9 de agosto de 2004

7. por el Subsecretario de Estado Especial, Estado de Nueva York

8. No. NYC-10299517A

9. Sello/Timbre 10. Firma

(El Gran Sello del Estado de Nueva York)

(Fdo.) James Bizzarri

James Bizzarri
Subsecretario de Estado Especial

La anterior es traducción fiel y completa del documento en referencia, de la cual se deja copia en este archivo para su confrontación.

MA. TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCION No. 01016
DE MINJUSTICIA

María Teresa Lara R.
c.c. 41.568.055 de Bogotá
Traductora Oficial según
Resolución No. 01016 del
2 de octubre de 1998, del
Ministerio de Justicia

DESPACHO NOTARIO ONCE DE ESTE CIRCULO HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
22 NOV 2005
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE (11)

000008

Apostille

(Convention de La Haye du 5 Octobre 1961)

1. Country: **United States of America**

   This public document

2. has been signed by **Norman Goodman**

3. acting in the capacity of **County Clerk**

4. bears the seal/stamp of the county of **New York**

Certified

5. At New York, New York 6. the 09th day of August 2004

7. by Special Deputy Secretary of State, State of New York

8. No. NYC-10299517A

9. Seal/Stamp 10. Signature

James Bizzarri
Special Deputy Secretary of State

041[illegible] (REV: [illegible])

DESPACHO NOTARIAL ONCE DE ESTE CÍRCULO HA SIDO COTEJAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
12 NOV. 2015
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

MARIA TERESA LARA R.
TRADUCTORA OFICIAL
RESOLUCIONES 994 DE 1979
DE MINJUSTICIA

215/04
078/05

COTEJO NOTARIAL

COMO NOTARIO ONCE DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

22 NOV 2005

BOGOTÁ D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

[redacted]

106 000010

Baker & McKenzie Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia
NIT: 860.068.940-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

LEGALIZE

POWER OF ATTORNEY

The undersigned,

PHARMACIA ITALIA S.p.A.

domiciled in

VIA ROBERT KOCH, 1.2
I-20152
MILANO, ITALY

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or OLGA GEORGETTE OTERO and/or RICARDO METIKE and/or JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6TH floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of

my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

PHARMACIA ITALIA S.p.A.

By Grover F. Fuller

Name typewritten: Grover F. Fuller, Jr.
Title: Authorized Attorney

Done and subscribed in New York, NY

On the 25 day of June of 2004

Signature of the person issuing the Power

PODER

La abajo firmada,

PHARMACIA ITALIA S.p.A.

domiciliada en

VIA ROBERT KOCH, 1.2
I-20152
MILÁN, ITALIA

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ and/or OLGA GEORGETTE OTERO and/or RICARDO METIKE and/or JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de:

mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en New York, NY

A los 25 días del mes de Junio de 2004

Firma de la persona que firma el Poder

NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL DOCUMENTO QUE SE TUVO A LA VISTA.
22 NOV 2005
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

107

PHARMACIA

Pharmacia & Upjohn S.p.A.
Via Robert Koch, 1.2
20152 Milano, Italia
telefono +39 0248381
telefax +39 0248382734

GENERAL POWER OF ATTORNEY

For anyone Grover F. Fuller Jr.

with the address Pfizer Inc.
150 East 42nd Street
NEW YORK, NY 10017-5612
U.S.A.

or anyone that he may appoint in his stead, to act as our representative in all countries, in matters in connection with applications for patents or designs or in connection with such protection granted, and on letters and documents in these matters be authorized to sign for the firm of PHARMACIA & UPJOHN SpA.

This power of attorney may be revoked at any time by a written instrument executed by a duly authorized officer of PHARMACIA & UPJOHN SpA.

Date 02/25/04

Emanuele Barié

President

COTEJO NOTARIAL ONCE DE ESTE CÍRCULO HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HA SIDO PUESTO A LA VISTA.
22 NOV 2005
BOGOTÁ D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

NOTARIAL CERTIFICATION

On this 24th day of June 20004, the undersigned Notary

CERTIFIES

1. That Grover F. Fuller, Jr. of legal age and domiciled in Via Robert Koch, 1.2 I- 20152 Milano, Italy set his hand on the foregoing document.
2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.
3. That the grantor has executed the foregoing document as Authorised Attorney of the judicial person PHARMACIA ITALIA S.p.A.
4. That the judicial person PHARMACIA ITALIA S.p.A. having its home office in VIA ROBERT KOCH, 1.2 I-20152 MILANO, ITALY is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.
5. That the grantor has in fact the aforesaid authority and that his/her representation is legal.
6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

Certificate of Incorporation No. 99073/8578 (14 September 2001).

COUNTY
Notary Public, State Of New York
No. 01CA4958877
Qualified in New York County
Commission Expires 12/11/2006

Notary Public

CERTIFICACION NOTARIAL

A los 24 días del mes de Junio de 2004, el suscrito Notario

DA FE

1 Que Grover F. Fuller, Jr. mayor y domiciliado en Via Robert Koch, 1.2 I-20152 Milano, Italia suscribió de su puño y letra el documento que antecede.
2 Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.
3 Que el otorgante ha suscrito el referido documento en su carácter de Abogado Autorizado de la persona jurídica PHARMACIA ITALIA S.p.A.
4 Que la persona jurídica PHARMACIA ITALIA S.p.A. con sede en VIA ROBERT KOCH, 1.2 I-20152 MILÁN, ITALIA está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.
5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.
6 Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

Certificado de Incorporación No. 99073/8578 (14 Septiembre 2001)

El Notario Público

DERECHO NOTARIO ONCE DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
22 NOV 2005
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

CLERK

NEW YORK

State of New York
County of New York,

Nº 389290

I, NORMAN GOODMAN, County Clerk and Clerk of the Supreme Court of the State of New York, in and for the County of New York, a Court of Record, having by law a seal,
DO HEREBY CERTIFY pursuant to the Executive Law of the State of New York, that

whose name is subscribed to the annexed affidavit, deposition, certificate of acknowledgment or proof, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York duly commissioned, sworn and qualified to act as such; that pursuant to law, a commission or a certificate of his official character, with his autograph signature, has been filed in my office; that at the time of taking such proof, acknowledgment or oath, he was duly authorized to take the same; that I am well acquainted with the handwriting of such NOTARY PUBLIC or have compared the signature on the annexed instrument with his autograph signature deposited in my office, and I believe that such signature is genuine.

IN WITNESS WHEREOF, I have hereunto set my hand affixed my official seal this

JUL 27 2004

FEE PAID $3.00

County Clerk and Clerk of the Supreme Court, New York County

DOY FE NOTARIAL QUE ESTE DOCUMENTO ES IGUAL AL PRESENTADO QUE ESTA FOTOCOPIA CORRESPONDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

22 NOV 2005

BOGOTA, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 December 2004 (02.12.2004)

PCT

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WO 2004/104007 A1

(51) International Patent Classification[7]: C07D 487/04, 487/14, A61K 31/519, A61P 35/00

(21) International Application Number: PCT/EP2004/050612

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/472,661 22 May 2003 (22.05.2003) US

(71) Applicant *(for all designated States except US)*: PHARMACIA ITALIA S.P.A. [IT/IT]; Via Robert Koch, 1.2, I-20152 Milan (Italy) (IT).

(72) Inventors; and

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(54) Title: PYRAZOLO-QUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS KINASE INHIBITORS

(57) Abstract: Pyrazolo-quinazoline derivatives of formula (Ia) or (Ib) as defined in the specification, and pharmaceutically acceptable salts thereof, process for their preparation and pharmaceutical compositions comprising them are disclosed; the compounds of the invention may be useful, in therapy, in the treatment of diseases associated with a disregulated protein kinase activity, like cancer.

(01079)

TITLE OF THE INVENTION

PYRAZOLO-QUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to pyrazolo-quinazoline derivatives, to a process for their preparation, to pharmaceutical compositions comprising them, and to their use as therapeutic agents, particularly in the treatment of cancer and cell proliferation disorders.

Discussion of the Background

Several cytotoxic drugs such as, e.g., fluorouracil (5-FU), doxorubicin and camptothecins, damage DNA or affect cellular metabolic pathways and thus cause, in many cases, an indirect block of the cell cycle. Therefore, by producing an irreversible damage to both normal and tumor cells, these agents result in a significant toxicity and side-effects.

In this respect, compounds capable of functioning as highly specific antitumor agents by selectively leading to tumor cell arrest and apoptosis, with comparable efficacy but reduced toxicity than the currently available drugs, are desirable.

It is well known that progression through the cell cycle is governed by a series of checkpoint controls, otherwise referred to as restriction points, which are regulated by a family of enzymes known as the cyclin-dependent kinases (cdk). In turn, the cdks themselves are regulated at many levels such as, for instance, binding to cyclins.

The coordinated activation and inactivation of different cyclin/cdk complexes is necessary for normal progression through the cell cycle. Both the critical G1-S and G2-M transitions are controlled by the activation of different cyclin/cdk activities. In G1, both cyclin D/cdk4 and cyclin E/cdk2 are thought to mediate the onset of S-phase. Progression through S-phase requires the activity of cyclin A/cdk2 whereas the activation of cyclin A/cdc2 (cdk1) and cyclin B/cdc2 are required for the onset of mitosis. For a general reference to cyclins and cyclin-dependent kinases see, for instance, Kevin R. Webster et al, in Exp. Opin. Invest. Drugs, 1998, Vol. 7(6), 865-887.

Checkpoint controls are defective in tumor cells due, in part, to disregulation of cdk activity. For example, altered expression of cyclin E and cdks has been observed in tumor cells, and deletion of the cdk inhibitor p27 KIP gene in mice has been shown to result in a higher incidence of cancer.

Increasing evidence supports the idea that the cdks are rate-limiting enzymes in cell cycle progression and, as such, represent molecular targets for therapeutic intervention. In particular, the direct inhibition of cdk/cyclin kinase activity should be helpful in restricting the unregulated proliferation of a tumor cell.

Further protein kinases known in the art as being implicated in the growth of cancer cells are the Aurora kinases, in particular Aurora-2.

Aurora-2 was found to be over-expressed in a number of different tumor types. Its gene locus maps at 20q13, a chromosomal region frequently amplified in many cancers, including breast [Cancer Res. 1999, 59(9) 2041-4] and colon.

20q13 amplification correlates with poor prognosis in patients with node-negative breast cancer and increased Aurora-2 expression is indicative of poor prognosis and decreased survival time in bladder cancer patients [J. Natl. Cancer Inst., 2002, 94(17) 1320-9]. For a general reference to Aurora-2 role in the abnormal centrosome function in cancer see also Molecular Cancer Therapeutics, 2003, 2, 589 – 595.

SUMMARY OF THE INVENTION

It is an object of the invention to provide compounds which are useful in treating cell proliferative disorders caused by and/or associated with an altered protein kinase activity, for instance Aurora 2 inhibitory activity and cell cycle dependent kinase activity. It is another object to provide compounds which have protein kinase inhibitory activity.

The present inventors have now discovered that certain pyrazolo-quinazolines are endowed with protein kinase inhibitory activity and are thus useful in therapy as antitumor agents and lack, in terms of both toxicity and side effects, the aforementioned drawbacks associated with currently available antitumor drugs.

More specifically, the pyrazolo-quinazolines of the invention are useful in the treatment of a variety of cancers including, but not limited to: carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder,

ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukaemia, acute lymphocitic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukaemias, myelodysplastic syndrome and promyelocytic leukaemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cell cycle kinases such as Aurora or cdks in the regulation of cellular proliferation, these pyrazolo-quinazoline derivatives are also useful in the treatment of a variety of cell proliferative disorders such as, for example, benign prostate hyperplasia, familial adenomatosis, polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

The compounds of the invention may be useful in treatment of Alzheimer's disease, as suggested by the fact that cdk5 is involved in the phosphorylation of tau protein (J. Biochem. 117, 741-749, 1995).

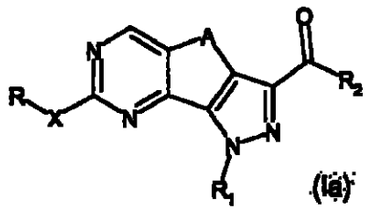
The compounds of this invention, as modulators of apoptosis, may also be useful in the treatment of cancer, viral infections, prevention of AIDS development in HIV-infected individuals, autoimmune diseases and neurodegenerative disorders.

The compounds of this invention may be useful in inhibiting tumor angiogenesis and metastasis, as well as in the treatment of organ transplant rejection and host versus graft disease.

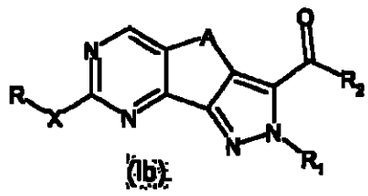
The compounds of the invention may also act as inhibitor of other protein kinases, e.g., protein kinase C in different isoforms, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, PI3K, weel kinase, Src, Abl, Akt, MAPK, ILK, MK-2, IKK-2, Cdc7, Nek, and thus be effective in the treatment of diseases associated with other protein kinases.

The compounds of the invention are also useful in the treatment and prevention of radiotherapy-induced or chemotherapy-induced alopecia.

Accordingly, in a first embodiment, the present invention provides a method for treating cell proliferative disorders caused by and/or associated with an altered protein kinase activity, like for instance Aurora 2 activity and cell cycle dependent kinase activity, by administering to a mammal in need thereof an effective amount of a pyrazolo-quinazoline derivative represented by formula (Ia) or (Ib)



(Ia)



(Ib)

wherein

R is hydrogen or an optionally substituted group selected from amino, straight or branched C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl;

X is a single bond or a divalent radical selected from -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- or $-SO_2-$, wherein R' is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R and R' may form a 5 to 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

R_1, bonded to any one of the nitrogen atoms of the pyrazole ring as per formulae (Ia) or (Ib), represents a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, in formula (Ib), R_1 is a divalent $-(CH_2)_n$-NH- group being linked to R_2, wherein n is 2 or 3;

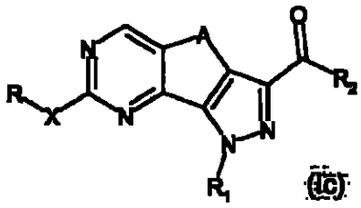
R_2 is a group selected from -NR"R"', -N(OH)R", -OR" or -R", wherein R" and R"' are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, together with the nitrogen atom to which they are

bonded, R'' and R''' may form a 5 to 6 membered heteroaryl or heterocyclyl group, optionally containing one additional heteroatom selected among N, O or S;

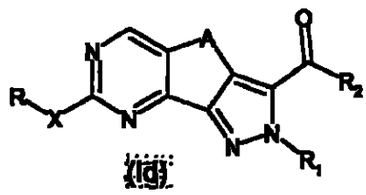
A is a divalent group selected from $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ or $-CH=CH-$;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention also provides a method for treating cell proliferative disorders caused by and/or associated with an altered protein kinase activity, like cell cycle dependent kinase activity, by administering to a mammal in need thereof an effective amount of a pyrazolo-quinazoline derivative represented by the above formula (Ia) or (Ib).



(Ic)



(Id)

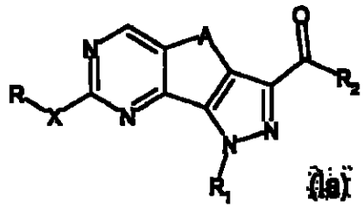
In a preferred embodiment of the methods described above, the cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

Specific types of cancer that may be treated include carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

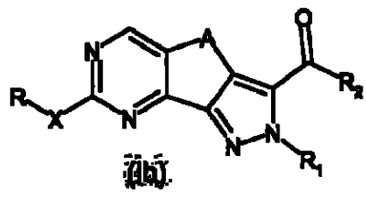
In another preferred embodiment of the method described above, the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis. In addition, the inventive method provides tumor angiogenesis and metastasis inhibition as well as treatment of organ transplant rejection and host versus graft disease. The inventive methods may also provide cell cycle inhibition or cdk/cyclin dependent inhibition.

In addition to the above, the methods object of the present invention provide treatment and prevention of radiotherapy-induced or chemotherapy-induced alopecia.

The present invention also provides a pyrazolo-quinazoline derivative represented by formula (Ia) or (Ib)



(Ia)



(Ib)

wherein

R is hydrogen or an optionally substituted group selected from amino, straight or branched C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl;

X is a single bond or a divalent radical selected from -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- or $-SO_2$-, wherein R' is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R and R' may form a 5 to 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

R_1, bonded to any one of the nitrogen atoms of the pyrazole ring as per formulae (Ia) or (Ib), represents a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, in formula (Ib), R_1 is a divalent $-(CH_2)_n$-NH- group being linked to R_2, wherein n is 2 or 3;

R_2 is a group selected from -NR"R'", -N(OH)R", -OR" or -R", wherein R" and R'" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R" and R'" may form a 5 to 6 membered heteroaryl or heterocyclyl group, optionally containing one additional heteroatom selected among N, O or S;

A is a divalent group selected from $-CH_2$-, $-(CH_2)_2$-, $-CH_2$-$C(CH_3)_2$-, $-C(CH_3)_2$-CH_2- or -CH=CH-;

or a pharmaceutically acceptable salt thereof.

The present invention also includes methods of synthesizing the pyrazolo-quinazoline derivatives represented by formulas (Ia) or (Ib) that, unless otherwise provided, may be conveniently grouped and defined as compounds of formula (I). Pharmaceutical compositions comprising the pyrazolo-quinazoline derivatives of formula (I) are also included in the present invention.

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Several heterocyclic compounds are known in the art as protein kinase inhibitors. As an example, 2-carboxamido-pyrazoles and 2-ureido-pyrazoles, and derivatives thereof, have been disclosed as protein kinase inhibitors in the international patent applications WO 01/12189, WO 01/12188, WO 02/48114 and WO 02/70515, all in the name of the applicant itself.

Fused bicyclic compounds comprising pyrazole moieties and possessing kinase inhibitory activity have been also disclosed in WO 00/69846, WO 02/12242 as well as WO 03/028720 and still unpublished US patent application 60/381092 (filed in May 17, 2002), all in the name of the applicant itself.

Fused tricyclic derivatives possessing kinase inhibitory activity are also disclosed in two copending applications PCT/EP03/01594 and PCT/US03/04844 (both claiming February 19, 2002 priority from US applications No. 60/357918 and No. 60/357960, respectively) and herewith incorporated by reference; none of the said applications specifically disclose the derivatives in re.

In addition, fused polycyclic pyrimidine derivatives as protein kinase inhibitors are also disclosed in the international patent applications WO 98/58926 and WO 98/28281, both in the name of Celltech Therapeutics Ltd; though comprised within the general formula of both applications, no specific examples of pyrazolo-quinazolines of the present invention are exemplified therein.

Finally, heterocyclic ring fused pyrimidine derivatives for the treatment of hyperproliferative diseases are disclosed in WO 96/40142 in the name of Pfizer Inc.

The compounds of formula (I) of the invention may have asymmetric carbon atoms and may therefore exist as individual optical isomers, as racemic admixtures or as any other admixture comprising a majority of one of the two optical isomers, which are all to be intended as within the scope of the present invention.

Likewise, the use as an antitumor agent of all the possible isomers and their admixtures and of both the metabolites and the pharmaceutically acceptable bio-precursors (otherwise referred to as pro-drugs) of the compounds of formula (I) are also within the scope of the present invention.

Prodrugs are any covalently bonded compounds which release the active parent drug, according to formula (I), in vivo.

In cases when compounds may exist in tautomeric forms, for instance keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

In the present description, unless otherwise specified, with the term straight or branched C_1-C_6 alkyl we intend any of the groups such as, for instance, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, and the like.

With the term C_3-C_{10} cycloalkyl we intend, unless otherwise provided, a cycloaliphatic ring such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, as well as any bridged cycloalkyl group with up to 10 carbon atoms.

The term aryl includes carbocyclic or heterocyclic hydrocarbons with from 1 to 2 ring moieties, either fused or linked to each other by single bonds, wherein at least one of the rings is aromatic; if present, any aromatic heterocyclic hydrocarbon also referred to as heteroaryl group, comprises a 5 to 6 membered ring with from 1 to 3 heteroatoms selected among N, O or S.

Examples of aryl groups according to the invention are, for instance, phenyl, biphenyl, α- or β-naphthyl, dihydronaphthyl, thienyl, benzothienyl, furyl, benzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, purinyl, quinolyl, isoquinolyl, dihydroquinolinyl, quinoxalinyl, benzodioxolyl, indanyl, indenyl, triazolyl, and the like.

Unless otherwise specified, the term heterocyclyl includes 5 to 6 membered saturated, partly unsaturated or fully unsaturated heterocycles with from 1 to 3 heteroatoms selected among N, O or S. Apart from the fully unsaturated heterocycles, previously

referred to as aromatic heterocycles and encompassed by the term aryl, examples of saturated or partly unsaturated heterocycles according to the invention are, for instance, pyran, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazolidine, pyrazoline, thiazoline, thiazolidine, dihydrofuran, tetrahydrofuran, 1,3-dioxolane, piperidine, piperazine, morpholine and the like.

From all of the above, it is clear to the skilled man that any compound of the invention wherein X represents a single bond has to be intended as having the R group directly linked to the pyrimidine moiety.

According to the above indicated substituent meanings and unless otherwise specified, any of the above R, R', R_1, R" and R"' group may be optionally substituted in any of their free positions by one or more groups, for instance 1 to 6 groups, independently selected from: halogen, nitro, oxo groups (=O), cyano, azido, alkyl, polyfluorinated alkyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, alkylaryl, alkylheterocyclyl, hydroxy, alkoxy, polyfluorinated alkoxy, aryloxy, arylalkyloxy, heterocyclyloxy, heterocyclylalkyloxy, methylenedioxy, alkylcarbonyloxy, alkylcarbonyloxyalkyl, arylcarbonyloxy, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, cycloalkyloxycarbonyl, amino, aminoalkyl, alkylaminoalkyl, alkylaminoalkyloxy, ureido, alkylamino, dialkylamino, arylamino, diarylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, alkoxycarbonylamino, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylthio and alkylthio.

In this respect, with the term halogen atom we intend a fluorine, chlorine, bromine or iodine atom.

With the term perfluorinated alkyl we intend any of the above straight or branched C_1-C_6 alkyl groups which are substituted by more than one fluorine atom such as, for instance, trifluoromethyl, trifluoroethyl, 1,1,1,3,3,3-hexafluoropropyl, and the like.

With the term alkoxy, aryloxy, heterocyclyloxy and derivatives thereof, e.g. perfluorinated alkoxy, we intend any of the above alkyl, aryl or heterocyclyl groups linked to the rest of the molecule through an oxygen atom (-O-).

From all of the above, it is clear to the skilled person that any group which name is a composite name such as, for instance, arylalkyl or heterocyclylalkyl has to be intended as conventionally construed by the parts from which it derives, e.g. by an alkyl group which is further substituted by aryl or heterocyclyl, wherein alkyl, aryl or heterocyclyl are as above defined.

Likewise, any of the terms such as, for instance, alkylthio, alkylamino, dialkylamino, alkoxycarbonyl, alkoxycarbonylamino, heterocyclylcarbonyl, heterocyclylcarbonylamino, cycloalkyloxycarbonyl and the like, include groups wherein the alkyl, alkoxy, aryl, cycloalkyl and heterocyclyl moieties are as above defined.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition salts with inorganic or organic acids, e.g., nitric, hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric, acetic, trifluoroacetic propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid, as well as the salts with inorganic or organic bases, e.g., alkali or alkaline-earth metals, especially sodium, potassium, calcium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines, preferably methylamine, ethylamine, diethylamine, triethylamine, piperidine and the like.

According to a first embodiment of the invention addressed to the compounds of formula (Ia) or (Ib), preferred derivatives are those wherein X is a group -NH- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

Also preferred are the compounds of formula (Ia) or (Ib) wherein X is a group -O- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

Also preferred are the compounds of formula (Ia) or (Ib) wherein X is a group -S- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an

optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

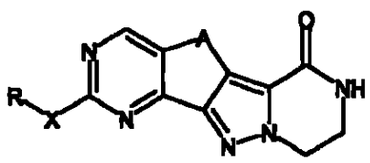
Even more preferred, within the above classes of compounds (Ia) or (Ib) are those same derivatives wherein A is a group $-(CH_2)_2-$.

According to another embodiment of the invention addressed to the compounds of formula (Ia) or (Ib), a class of preferred compounds is represented by those derivatives wherein X is a group -NH- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

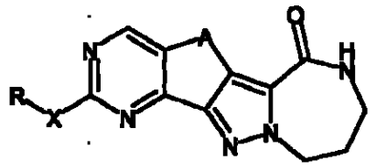
Another class of preferred compounds of the invention of formula (Ia) or (Ib) is represented by the derivatives wherein X is a group -O- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

Another class of preferred compounds of the invention of formula (Ia) or (Ib) is represented by the derivatives wherein X is a group -S- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

Another class of preferred compounds of the invention of formula (Ib) is represented by the derivatives wherein R, X and A are as above defined and R_1 and R_2 are linked together through a divalent $-(CH_2)_n$-NH- group so as to give rise to:



n=2



n=3

Also preferred, within the above class of derivatives of formula (Ia) and (Ib), are the compounds wherein A is a group selected from $-CH_2-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$.

For a reference to any specific compound of formula (Ia) or (Ib) of the invention, optionally in the form of a pharmaceutically acceptable salt, see the experimental section and claims.

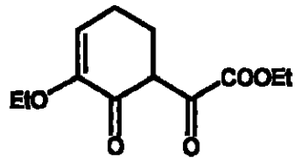
As formerly indicated, a further object of the present invention is represented by the process for preparing the compounds of formula (I) which formula, unless otherwise

specifically provided, has to be intended as comprising the derivatives of formula (Ia) and (Ib).

Therefore, the compounds of formula (I) or the pharmaceutically acceptable salts thereof may be obtained by a process comprising:

(1) when A is a $-(CH_2)_2-$ group:

st.1) reacting 2-ethoxy-2-cyclohexen-1-one with diethyl oxalate, in the presence of lithium (bis-trimethylsilyl)amide [$LiN(TMS)_2$], so as to obtain a compound of formula (II)



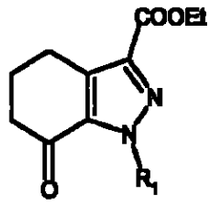
(II);

and treating it with a hydrazine derivative of formula (III)

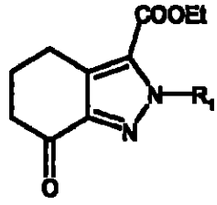
$$R_1\text{-}NHNH_2 \quad (III)$$

wherein R_1 has the above reported meanings, according to the operative conditions set forth in any one of the steps (st.2a), (st.2b) or (st.2c)

st.2a) in the presence of a lower alcohol so as to obtain a mixture of the compounds of formula (IVa) and (IVb)



(IVa)



(IVb);

wherein R_1 is as above reported, and separating their mixture into the single compounds (IVa) and (IVb);

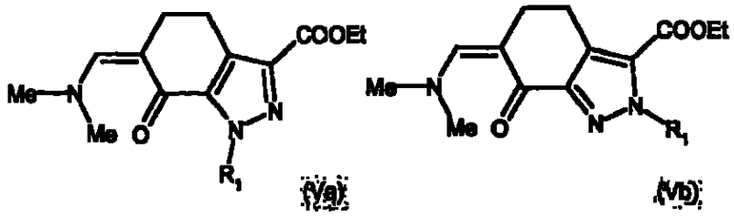
st.2b) in the presence of acetic acid so as to obtain a compound of formula (IVa);

st.2c) by alkylating a compound of formula (IVa) being obtained in step (st.2a) or (st.2b) and wherein R_1 is hydrogen with the compounds of formula (IVc)

$$R_1Y \quad (IVc)$$

wherein Y is a suitable leaving group such as mesyl, tosyl, halogen, so to obtain a mixture of compounds of formula (IVa) and (IVb) wherein R_1 is as above reported and separating their mixture into the compounds (IVa) and (IVb);

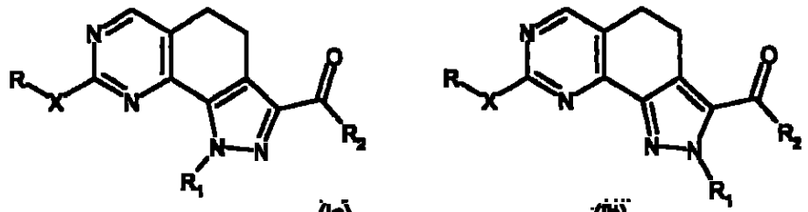
st.3) reacting the compound of formula (IVa) prepared according to any one of steps (st.2a), (st.2b) or (st.2c), or of formula (IVb) prepared according to steps (st.2a) or (st.2c), with dimethylformamide-di-tert-butylacetale so as to obtain a compound of formula (Va) or (Vb)



(Va) (Vb)

wherein R_1 is as above reported; and reacting the compound of formula (Va) or (Vb) according to any one of the alternative steps (st.4a), (st.4b) or (st.4c)

st.4a) with guanidine so as to obtain a compound of formula (Ia) or (Ib)



(Ia) (Ib)

wherein R-X- is amino, R_2 is ethoxy, and R_1 is as above defined; and optionally converting them into other derivatives of formula (I);

st.4b) with a guanidine derivative of formula (VI)

$$R\text{-}NH\text{-}C(=NH)NH_2 \quad (VI)$$

wherein R is as above reported, so as to obtain a compound of formula (Ia) or (Ib) wherein R and R_1 are as above reported, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

st.4c) with an alkylisothiourea of formula (VII)

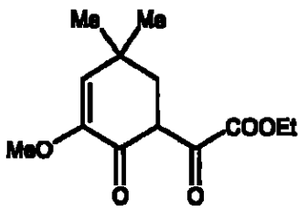
$$R\text{-}S\text{-}C(=NH)NH_2 \quad (VII)$$

wherein R is as above reported, so as to obtain a compound of formula (Ia) or (Ib) wherein R and R_1 are as above reported, X is -S- and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

st.4d) with methylisourea so as to obtain a compound of formula (Ia) or (Ib) wherein R_1 is as above reported R is methyl, X is -O- and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

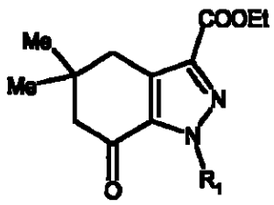
(2) when A is a $-C(CH_3)_2-CH_2-$ group:

st.5) reacting 2-methoxy-4,4-dimethyl-2-cyclohexen-1-one with diethyl oxalate, in the presence of $[LiN(TMS)_2]$, so as to obtain a compound of formula (VIII)

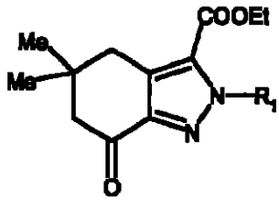


(VIII);

st.6) reacting the compound of formula (VIII) with a hydrazine derivative of formula (III) according to any one of previous steps (st.2a) or (st.2b) so as to obtain the compound of formula (IXa) or (IXb)



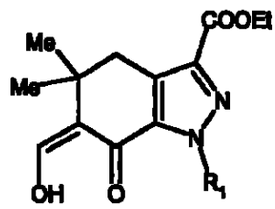
(IXa);



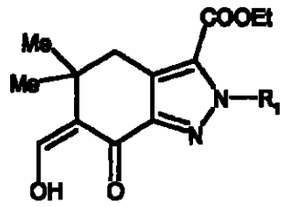
(IXb);

wherein R_1 is as above reported;

st.7) reacting the compound of formula (IXa) or (IXb) with ethyl formate under basic conditions, so as to obtain the compound of formula (Xa) or (Xb)

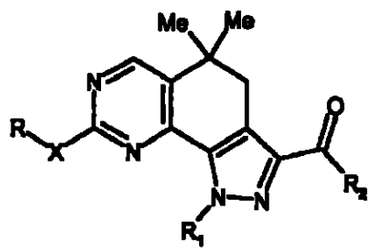


(Xa);

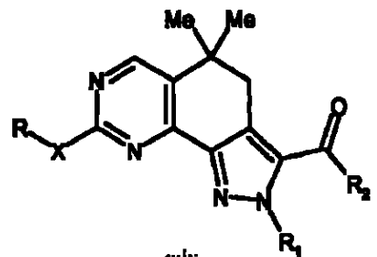


(Xb);

st.8) reacting the compound of formula (Xa) or (Xb) with guanidine or a guanidine derivative of formula (VI), so as to obtain a compound of formula (Ia) or (Ib)



(Ia)

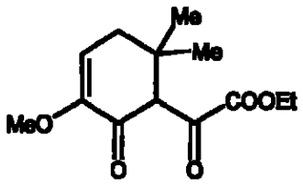


(Ib)

wherein R and R_1 are as above reported, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

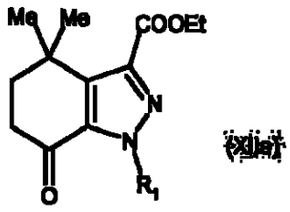
(3) when A is a $-CH_2-C(CH_3)_2-$ group:

st.9) reacting 2-methoxy-5,5-dimethyl-2-cyclohexen-1-one with diethyl oxalate in the presence of sodium hydride, so as to obtain the compound of formula (XI)

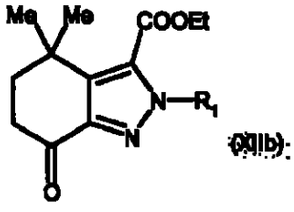


(XI)

st.10) reacting the compound of formula (XI) with a hydrazine derivative of formula (III) according to any one of previous steps (st.2a) or (st.2b) so as to obtain the compound of formula (XIIa) or (XIIb)



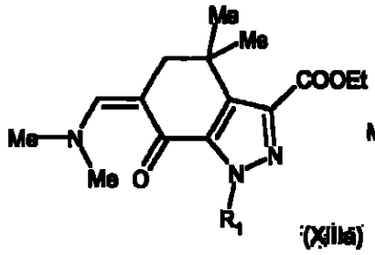
(XIIa)



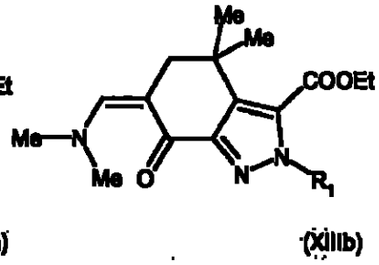
(XIIb)

wherein R_1 is as above reported;

st.11) reacting the compound of formula (XIIa) or (XIIb) with dimethylformamide-di-tert-butylacetale so as to obtain a compound of formula (XIIIa) or (XIIIb)

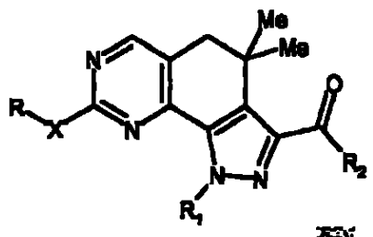


(XIIIa)

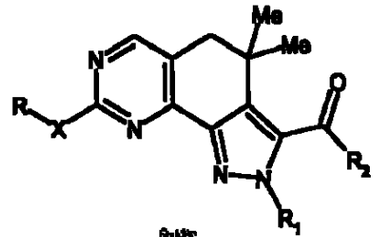


(XIIIb)

st.12) reacting the compound of formula (XIIIa) or (XIIIb) with guanidine or a guanidine derivative of formula (VI), so as to obtain a compound of formula (Ia) or (Ib)



(Ia)

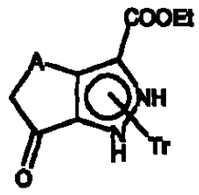


(Ib)

wherein R and R_1 are as above reported, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

(4) when, in formula (Ib), A is a $-(CH_2)_2-$ group, $-CH_2-C(CH_3)_2-$ group, $-C(CH_3)_2-CH_2-$ group, R_1 is directly linked to R_2 so as to yield a tetra-cyclic ring structure:

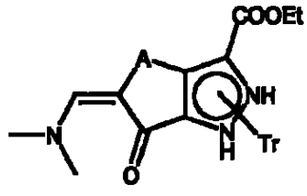
st.13) reacting a compound of formula (IV), (IX), (XII) wherein R_1 is hydrogen, obtained according to (st.2), (st.6), (st.10) of the process, with triphenylmethyl chloride so as to obtain a compound of formula (XIV)



(XIV)

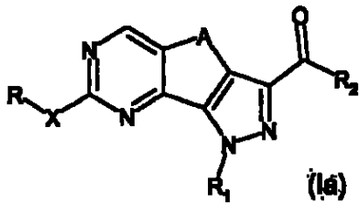
wherein Tr stands for trityl (triphenylmethyl);

st.14) reacting the compound of formula (XIV) with dimethylformamide-di-tert-butylacetale, as set forth in step (st.3), so as to obtain a compound of formula (XV)

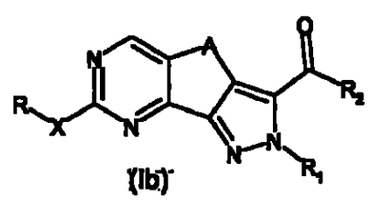


(XV)

st.15) reacting the compound of formula (XV) with a suitable guanidine derivative of formula (VI), as set forth in step (st.4b), so as to obtain a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

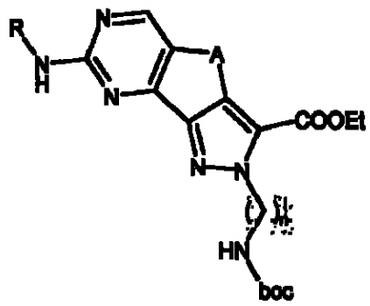
wherein R is as above defined, A is a $-(CH_2)_2-$ group, $-CH_2-C(CH_3)_2-$ group, $-C(CH_3)_2-CH_2-$ group, X is NH, R_1 is trityl and R_2 is ethoxy;

st.16) reacting the above compound of formula (Ia) or (Ib) under acidic conditions, so as to obtain the corresponding compound of formula (Ia) or (Ib) wherein R_1 is hydrogen;

st.17) reacting the above compound of formula (Ia) or (Ib) with a suitable alkylating agent of formula (XVI) in the presence of litium tert-butylate

$$Br-(CH_2)_n-NH-BOC \quad (XVI)$$

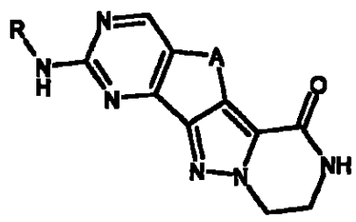
wherein n is 2 or 3, so as to obtain a compound of formula (Ib)



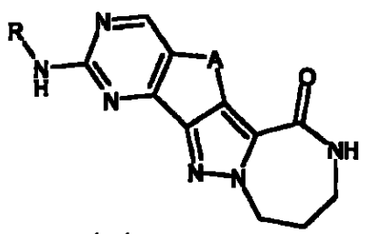
(Ib)

wherein A, n and R are as above defined;

st.18) reacting the above compound of formula (Ib) under acidic conditions, so as to convert the tert-butoxycarbonylamino group into amino (deprotection) and reacting it with cesium carbonate ($CsCO_3$) so as to obtain any one of the two compounds of formula (Ib)



(Id; n=2)

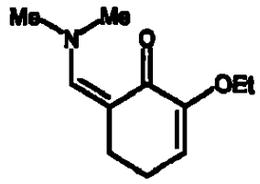


(Id; n=3)

wherein A and R is as above defined, and optionally converting them into other derivatives of formula (I);

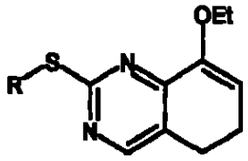
(5) when R_2 is a bulky group:

st.19) reacting 2-ethoxy-2-cyclohexenone with dimethylformamide-di-tert-butylacetale, as reported in step (st.3), so as to obtain a compound of formula (XVII)



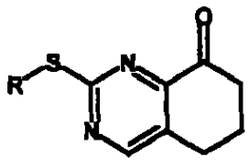
(XVII)

st.20) reacting the compound of formula (XVII) with a derivative of formula (VII), according to step (st.4c), so as to obtain a compound of formula (XVIII)



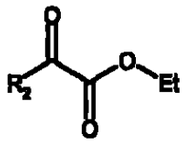
(XVIII)

wherein R is as above defined; and subsequently treating it under acidic conditions so as to obtain a compound of formula (XIX)



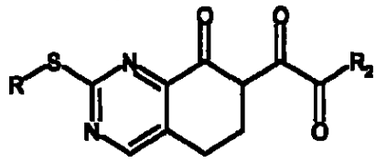
(XIX)

st.21) reacting the compound of formula (XIX) with a compound of formula (XX)



(XX)

wherein R_2 is a bulky group, so as to obtain a compound of formula (XXI)



(XXI)

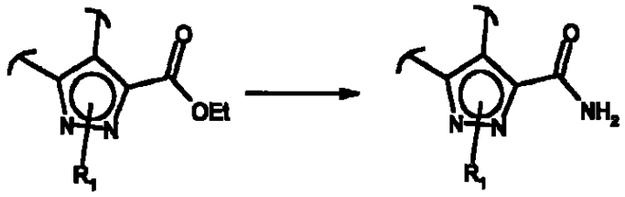
st.22) reacting the compound of formula (XXI) with a hydrazine derivative of formula (III), as per step (st.1) of the process, so as to obtain a compound of formula (I) wherein R and R_1 are as above defined, X is -S- and R_2 is a bulky group; and optionally converting them into other derivatives of formula (I).

As above reported, the compounds of formula (I) which are prepared according to the process object of the invention, for instance as set forth in steps (st.4a), (st.4b), (st.4c),

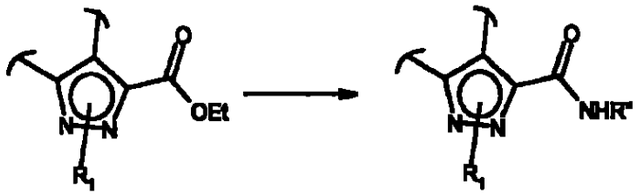
(st.8), (st.12), (st.13), (st.18) and (st.22), can be conveniently converted into other compounds of formula (I) by operating according to well-known operative conditions.

As an example, the compounds of formula (I):

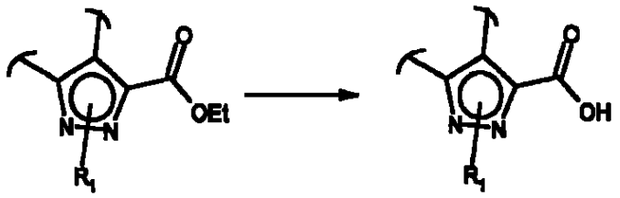
st.23) wherein R_2 is ethoxy may be converted into the compounds of formula (Ia) or (Ib) wherein R_2 is amino by treatment with ammonium hydroxide



st.24) wherein R_2 is ethoxy may be converted into the compounds of formula (I) wherein R_2 is a group -NHR" by treatment with an amine of formula R"-NH_2 (XXII)



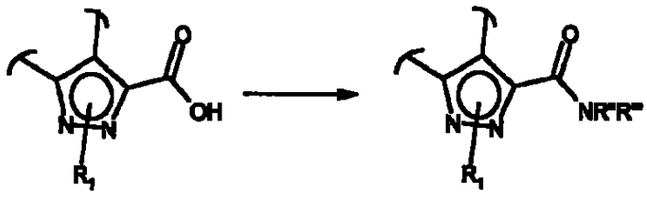
st.25) wherein R_2 is ethoxy may be converted into the compounds of formula (I) wherein R_2 is a group -OH through acidic or basic hydrolysis



st.26) wherein R_2 is -OH may be converted into the compounds of formula (I) wherein R_2 is a group -NR"R'" or -N(OH)R", through reaction with a derivative of formula (XXIII) or (XXIV)

R"R'"NH (XXIII) R"NHOH (XXIV)

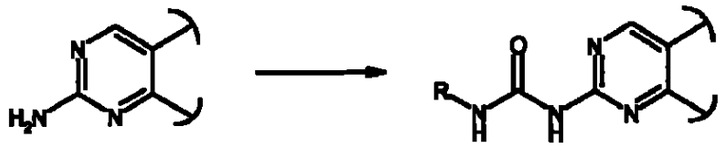
under basic conditions and in the presence of a suitable condensing agent



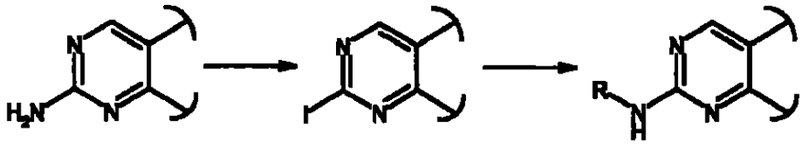
st.27) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is other than hydrogen, as above defined, and X is -CONH-, through reaction with an acid halide, for instance chloride, of formula R-COCl (XXV)



st.28) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is other than hydrogen, as above defined, and X is -NH-CO-NH-, through reaction with an isocyanate of formula R-NCO (XXVI)



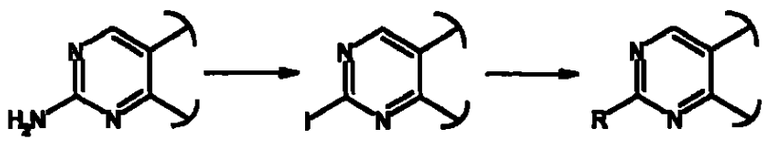
st.29) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is aryl and X is -NH-, by first converting the amino group to iodine with iso-amylnitrite and diiodomethane or cesium iodide, in the presence of iodine and CuI, and by subsequently reacting the iododerivative with an arylamine of formula R-NH_2 (XXVII), in the presence of palladium acetate and (2,2'-bis(diphenylphosphino))-1,1'-binaphthalene (BINAP)



st.29a) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is alkyl, cycloalkyl, cycloalkyl-alkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, and X is -NH-, by first converting the amino group to iodine, as described in the previous step (st.29), and by subsequently reacting the iododerivative with an alkyl, cycloalkyl, cycloalkyl-alkyl, arylalkyl, heterocyclyl or heterocyclylalkyl amine of formula RNH_2 (XXVII), wherein R is as therein defined;

st.30) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is aryl and X is a single bond, by first converting the amino group to iodine, as per the above step (st.29), and by subsequently reacting the iododerivative

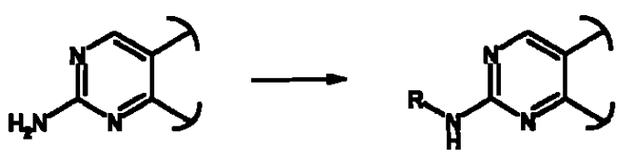
with an arylboronic acid of formula R-B(OH)$_2$ (XXVIII), in the presence of a palladium derivative



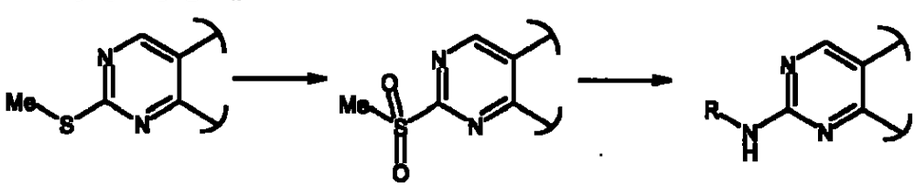
st.31) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is alkyl or arylmethyl, by reaction with an alkyl aldehyde or aryl-aldehyde of formula R-CHO (XXIX) in the presence of sodium cyanoborohydride ($NaBH_3CN$) and acetic acid



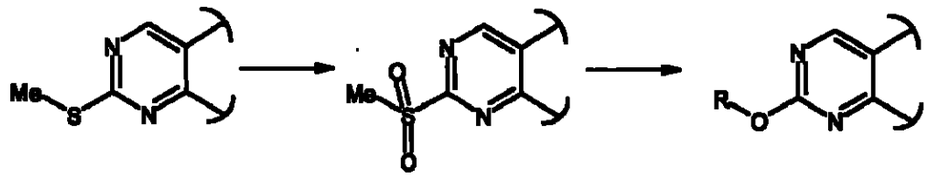
st.31a) wherein R is hydrogen and X is -NH- may be converted into the compounds of formula (I) wherein R is cycloalkyl or heterocycloalkyl, by reaction with an cycloalkyl ketone or heterocycloalkylketone in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$) and trifluoroacetic acid



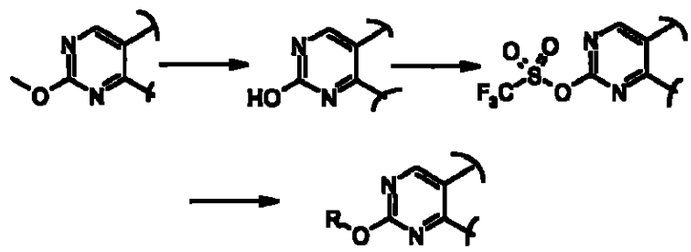
st.32) wherein R is as above defined, e.g. methyl, and X is -S- may be converted into the compounds of formula (I) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, arylalkyl or heterocyclylalkyl group, by first converting the RS- group into RSO_2- under oxidative conditions, and by then reacting the sulfonyl derivative with an amine of formula R-NH_2 (XXVII) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, arylalkyl or heterocyclylalkyl group



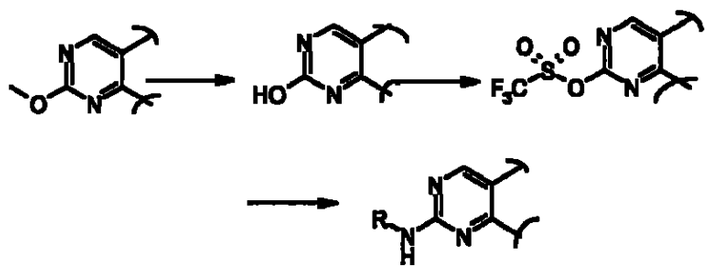
st.33) wherein R is as above defined, e.g. methyl, and X is -S- may be converted into the compounds of formula (I) wherein R is as defined in formula (I) and X is -O-, by first converting the RS- group into RSO_2- as per step (st.32) and by then reacting the sulfonyl derivative with a compound of formula R-OH (XXX)



st.33a) wherein R is methyl, and X is -O- may be converted into the compounds of formula (I) wherein R is as defined in formula (I) and X is -O-, by first converting the MeO- group into HO-, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with a compound of formula R-OH (XXX)



st.33b) wherein R is methyl and X is -O- may be converted into the compounds of formula (I) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, heterocyclylalkyl group, and X is -NH-, by first converting the MeO- group into HO-, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with an amine of formula $R\text{-}NH_2$ (XXVII) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, arylalkyl or heterocyclylalkyl group



st. 33c) wherein R is methyl and X is -O- may be converted into the compounds of formula (I) wherein R is an aryl and X is -NH-, by first converting the MeO- group into –OH, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with an amine of formula RNH_2 (XXVII) wherein R is an optionally substituted aryl in the presence of palladium acetate and BINAP;

st.34) wherein A is a $-(CH_2)_2-$ group may be converted into the compounds of formula (I) wherein A is a -CH=CH- group, under dehydrogenating operative conditions in the presence of a Pd or Pt catalyst.

The above process, in any one of the aforementioned variants, is an analogy process which can be carried out according to well known methods known in the art.

According to steps (st.1) of the process, 2-ethoxy-2-cyclohexen-1-one is reacted with diethyl oxalate in the presence of $LiN(TMS)_2$ and of a suitable solvent such as, for instance, dioxane, tetrahydrofuran or diethyl ether.

According to step (st.2a), the compound of formula (II) is reacted with a suitable hydrazine derivative of formula (III), in the presence of a lower alcohol such as methanol, ethanol or admixtures thereof. Preferably, the above reaction is carried out in ethanol at refluxing temperature, so as to obtain a mixture of both compounds of formula (IVa) and (IVb) wherein the former is present in major amounts. Their separation into the single compounds (IVa) and (IVb) is carried out under conventional methods, for instance through preparative HPLC.

By working according to step (st.2b) of the process, instead, that is by reacting the compound of formula (II) with the hydrazine derivative of formula (III) in the presence of acetic acid, a single compound of formula (IVa) is obtained. The reaction is preferably carried out at room temperature.

According to step (st.2c) of the process, the compound of formula (IVa) wherein R_1 is hydrogen, is reacted with a suitable compound of formula (IVc) in the presence of a base such as sodium hydride in a suitable solvent, for instance tetrahydrofuran, dioxane or dimethylformamide, at a temperature ranging from room temperature to 100°C, so as to obtain a mixture of compounds (IVa) and (IVb) wherein the former is present in major amounts, and by separating them under conventional methods, for instance through preparative HPLC.

According to step (st.3) of the process, the compound of formula (IVa) or (IVb) is reacted with dimethylformamide-di-tert-butylacetale, in the presence of a suitable solvent such as, for instance, dimethylformamide, so as to get the compounds of formula (Va) or (Vb), respectively. Preferably, the reaction is carried out at a temperature ranging from room temperature to about 70°C.

According to any one of the alternative steps (st.4a), (st.4b), (st.4c) or (st.4d) of the process, the compound of formula (Va) or (Vb) is reacted with guanidine, guanidine salts or derivatives thereof, alkylisothiourea or methylisourea so as to obtain the corresponding compound of formula (Ia) or (Ib) through pyrimidine ring formation. Any of the above reactions is carried out according to conventional methods. As an example, the reactions with guanidine or salts thereof such as hydrochloride, carbonate or nitrate, or with the guanidine derivative of formula (VI), as set forth in steps (st.4a) or (st.4b), are carried out in a lower alcoholic solvent under neutral or basic conditions, preferably with ethanol and sodium ethylate or with diazabicycloundecene (DBU) at refluxing temperature or, alternatively, in dimethylformamide at a temperature ranging from 80°C to refluxing temperature in the presence of potassium carbonate. The reaction with alkylisothiourea (VII), in (st.4c), is carried out in the presence of potassium acetate and in a suitable solvent such as dimethylformamide at refluxing temperature.

The reaction with methylisourea (st.4d) is carried out in a suitable solvent such as acetonitrile and in the presence of a base such as potassium carbonate at refluxing temperature.

The reactions of steps (st.5) and (st.6) are carried out under the operative conditions set forth in steps (st.1), (st.2a) or (st.2b) and lead to the desired compounds of formula (IXa) or (IXb), respectively.

Step (st.7) of the process is preferably carried out by reacting the derivative of formula (IXa) or (IXb) with ethyl formate under basic conditions, preferably in the presence of sodium ethylate or sodium hydride and of a suitable solvent such as, for instance, diethyl ether, tetrahydrofuran or dioxane, at a temperature ranging from room temperature to refluxing temperature.

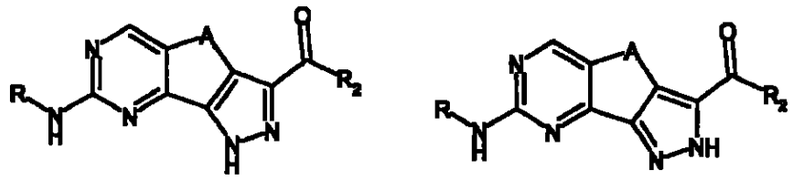
The reaction conditions of step (st.8) are those previously reported for steps (st.4a and st.4b).

According to step (st.9), 2-methoxy-5,5-dimethyl-2-cyclohexen-1-one is reacted with diethyl oxalate in the presence of sodium hydride and in a suitable solvent such as diethyl ether, tetrahydrofuran or dioxane, at refluxing temperature.

The subsequent reaction conditions of steps (st.10) are essentially those previously reported for steps (st.2a) or (st.2b), and those of steps (st.11) and (st.12) correspond to those of (st.3) and (st.4a and st.4b), respectively.

According to step (st.13) of the process, it is clear to the skilled man that both compounds of formula (IVa) or (IVb) wherein R_1 is a hydrogen atom are tautomeric forms of a given compound which can be conveniently identified as having formula (IV). In this respect, this same derivative is reacted with triphenylmethyl chloride so as to obtain a compound of formula (XIV) wherein either one of the two pyrazole nitrogen atoms are alkylated with a trityl (e.g. triphenylmethyl) group.

The operative conditions in steps (st.14) and (st.15) of the process essentially correspond to those already reported for steps (st.3) and (st.4a and st.4b). According to step (st.16), the trityl group of the compounds of formula (I) is removed under acidic conditions, for instance with trifluoroacetic acid and in the presence of a suitable solvent such as dichloromethane, so as to give rise to the corresponding compound of formula (I) wherein R_1 is hydrogen, in both forms:



Its subsequent alkylation with a derivative of formula (XVI), according to step (st.17) of the process, allows to selectively alkylate the pyrazole nitrogen atom which is in proximity of the -COOEt group; this reaction may be carried out with lithium tert-butylate and in a suitable solvent, such as dioxane, diethyl ether or tetrahydrofuran.

According to step (st.18), the above compound is first converted into the free amino derivative by working according to conventional methods, for instance under acidic conditions, preferably with hydrochloric acid, in a suitable solvent such as dioxane at refluxing temperature, and subsequently cyclised to the desired tetracyclic derivative in

the presence of a base such as cesium carbonate ($CsCO_3$) and in a suitable solvent such as a lower alcohol, preferably methanol, ranging from room temperature to reflux.

The operative conditions of steps (st.19) and (st.20) of the process essentially correspond to those already reported for steps (st.3) and (st.4c); the subsequent acidic treatment of the compound of formula (XVIII) to the compound of formula (XIX) is preferably carried out with an aqueous solution of acetic acid, at a temperature of about 100°C.

According to step (st.21), the compound of formula (XIX) is reacted with a suitable derivative of formula (XX) in the presence of sodium hydride and in a suitable solvent, e.g. diethyl ether, tetrahydrofuran or dioxane, at a temperature ranging from about -50°C to room temperature.

The operative conditions of step (st.22) essentially correspond to those of step (st.1) of the process.

As formerly indicated, the compounds of formula (I) thus prepared may be easily converted into several other compounds of formula (I) of the invention.

As an example, compounds of formula (I) bearing R_2 as an ethoxy group, or even as an alkoxy group, can be converted into a variety of derivatives according to methods well-known in the art to convert carboxyester groups (-$COOR_2$) into carboxamides (-$CONH_2$), N-substituted carboxamides (-CONHR") and carboxylic acids (-COOH), for instance as reported in steps (st.23), (st.24) and (st.25).

The operative conditions are those widely known in the art and may comprise, for instance in the conversion of a carboxyester group into a carboxamide group, the reaction with ammonia or ammonium hydroxide in the presence of a suitable solvent such as a lower alcohol, dimethylformamide or mixtures thereof; preferably the reaction is carried out with ammonium hydroxide in a methanol/dimethylformamide mixture, at a temperature ranging from about 50°C to about 100°C.

Analogous operative conditions apply in the preparation of N-substituted carboxamides wherein a suitable primary amine is used in place of ammonia or ammonium hydroxide.

Likewise, carboxyester groups may be converted into carboxylic acid derivatives through basic or acidic hydrolysis conditions, widely known in the art.

According to step (st.26) of the process, compounds of formula (I) wherein R_2 is hydroxy (-COOH) may be converted into carboxamido derivatives (-CONR"R"') or

[-CON(OH)R'''] wherein R'' and R''' are as formerly indicated, also inclusive of compounds wherein R'' and R''' form, together with the nitrogen atom to which they are bonded, a 5 or 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S.

The reaction is carried out in the presence of an amine of formula (XXIII) or of a compound of formula (XXIV), as the case may be, under basic conditions, preferably with N,N-diisopropyl-N-ethylamine or triethylamine, in a suitable solvent such as dichloromethane, dimethylformamide, tetrahydrofuran, or dioxane, and in the presence of a suitable condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylisouronium tetrafluoroborate (TBTU); catalytic amounts of (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) ma be also required.

In addition, compounds of formula (I) wherein R-NH- is an amino ($-NH_2$) group may be easily converted into the corresponding carboxamido (-NHCOR) or ureido (-NHCONHR) derivatives, as set forth in steps (st.27) or (st.28) of the process, respectively. Typically, the reaction with isocyanate is performed with sodium hydride in dimethylformamide whilst the one with the acid chloride may be carried out in a suitable solvent such as pyridine, tetrahydrofuran, ethyl acetate or dioxane, or a mixture of them at room temperature.

Compounds of formula (I) wherein R-NH- represents an arylamino or heteroarylamino group, can be obtained by the corresponding iodo derivatives which, in their turn, may be prepared by the corresponding compounds of formula (I) wherein R-NH- is amino, as per step (st.29) of the process.

The preparation of the iodo derivatives may be carried out in a suitable solvent such as tetrahydrofuran, diethyl ether or dimethoxyethane, at a temperature ranging from room temperature to about 70°C, and for a time of about 8 hours to about 48 hours.

The subsequent conversion of the iododerivative may be carried out in a suitable solvent such as dimethylformamide, dimethoxyethane or acetonitrile and in the presence of catalytic amounts of palladium acetate, (2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (BINAP) and a base such as potassium carbonate, potassium phosphate or cesium

carbonate, at a temperature ranging from room temperature to 110°C and for a time ranging from about 2 to about 24 hours.

Compounds of formula (I) wherein R is aryl and X is a single bond can be obtained, as reported in step (st.30), from the iodo derivative above mentioned by reaction with arylboronic acids of formula (XXVIII) in a suitable solvent such as dimethylformamide, dichloromethane, methanol, dimethoxyethane or acetonitrile, in the presence of tris(dibenzylideneacetone)dipalladium (0) or tetrakis triphenylphosphino palladium [$Pd(PPh_3)_4$], optionally in the presence of cesium fluoride, at a temperature ranging from room temperature to 100°C.

Compounds of formula (I) wherein RNH- represents an alkylamino, cycloalkylamino, cycloalkyl-alkylamino, heterocyclylamino, heterocyclylalkylamino can be obtained from the corresponding iodo derivative as set forth in step (st.29a) of the process. The reaction may be carried out in a suitable solvent such as dimethylformamide, dioxane or acetonitrile or without solvent at a temperature ranging from 40°C to 120°C for a time ranging from 3 to 18 hours.

Compounds of formula (I) wherein R-NH- is amino may be also converted into the corresponding alkylamino or arylmethylamino derivatives of formula (I) as reported in (st.31), by operating in a suitable solvent or in a mixture of solvents, for instance comprising a 1:1:1 mixture of acetic acid, methanol and water.

Compounds of formula (I) wherein R-NH- is amino may be also converted into the corresponding cycloalkylamino or heterocycloalkylamino derivatives of formula (I) as reported in (st.31a), by operating in a suitable solvent such as methylene chloride, acetonitrile, dimethylformamide.

Compounds of formula (I) wherein R-X- represents an alkylthio group (R-S-) may be converted into a variety of compounds of formula (I) wherein X is -NH-, by first oxidizing the alkylthio to alkylsulfonyl group and by replacing it with a R-NH- group, as reported in (st.32). The oxidative step may be carried out with oxone in the presence of a suitable solvent, preferably dimethylformamide or dimethylsulfoxide at room temperature; the subsequent replacement of the alkylsulfonyl group with a suitable amino derivative is preferably carried out in the presence of dimethylsulfoxide, dimethylformamide, dimethoxyethane, dioxane, acetonitrile, N-methyl-pyrrolidone or diglyme, at a temperature ranging from room temperature to about 100°C.

Interestingly, when the last step is carried out in the presence of dimethylsulfoxide as a suitable solvent, this same solvent can also act as oxidizing agent capable of furnishing the desired compounds wherein A represents a group -CH=CH-. These latter derivatives are then separated from the reaction mixture according to conventional methods, for instance by chromatography or by preparative HPLC.

According to step (st.33) of the process, compounds of formula (I) wherein X is -O- may be easily obtained by reacting the sulfonyl derivative with an alcohol or phenol derivative of formula (XXX) wherein R is as in formula (I). The reaction may be carried out in the presence of a base such as potassium or sodium carbonate, butyl lithium, lithium amide, sodium hydride or the like, in a suitable solvent such as dimethylformamide or tetrahydrofuran, and by working at a temperature ranging from room temperature to about 100°C.

Alternatively, according to steps (st.4d) and (st.33a), compounds of formula (I) wherein X is -O- may be obtained by reacting the compounds of formula (Va) and (Vb) with methylisourea sulfate by operating in a suitable solvent such as dioxane, dimethylformamide or acetonitrile in the presence of a base such as sodium or potassium carbonate at a temperature ranging from 50°C to 100°C. The compounds of formula (I) wherein X is -O- and R is hydrogen may be obtained by reacting the compounds of formula (I) wherein X is -O- and R is methyl with trimethylsilyl chloride in the presence of sodium iodide and in a suitable solvent such as dioxane, tetrahydrofuran or acetonitrile at room temperature. The compounds of formula (I) wherein X is -O- ans R is a trifluorosulfonyl group may be obtained by reacting the compounds of formula (I) wherein X is -O- and R is hydrogen with a triflating agent such as trifluoromethanesulfonic anhydride, trifluoromethanesulfonylchloride or N-phenyl-bis(trifluoromethanesulfonimide), optionally in the presence of a base such as triethylamine or N,N-diisopropyl-N-ethylamine (DIPEA), in a suitable solvent such as dichloromethane, tetrahydrofuran or dioxane at a temperature ranging from -78°C to room temperature.

The compounds of formula (I) wherein X is -O- and R is as described above may be obtained by reacting the compounds of formula (I) wherein X is -O- and R is a trifluoromethanesulfonyl group with an alcohol or phenol of formula (XXX) wherein R is as in formula (I), by operating in a suitable solvent such as dioxane, tetrahydrofuran,

dimethoxyethane, acetonitrile, dimethylformamide or dimethylsulfoxide, at a temperature ranging from room temperature to about 90°C, optionally in the presence of a base such as potassium carbonate, potassium terbutoxide or sodium hydride.

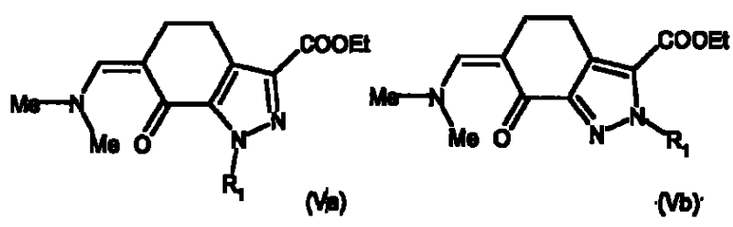
Alternatively the reaction may be carried out in a suitable solvent such as toluene, dimethylformamide, dimethoxyethane or acetonitrile, in the presence of palladium acetate, (±)-BINAP and a base such as potassium phosphate (K_3PO_4) or potassium or cesium carbonate (K_2CO_3 or $CsCO_3$) at a temperature ranging from 0°C to 100°C (st.33c).

The compounds of formula (I) wherein X is -NH- and R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl or a heterocyclylalkyl group may be obtained by reacting the compounds of formula (I) wherein X is -O- and R is a trifluoromethanesulfonyl group with an amine of formula $R\text{-}NH_2$ (XXVII) wherein R is as in formula (I), by operating in a suitable solvent such as dioxane, tetrahydrofuran, dimethoxyethane, acetonitrile, dimethylformamide or dimethylsulfoxide, at a temperature ranging from room temperature to 90°C, optionally in the presence of a base such as potassium carbonate or triethylamine.

Finally, any of the above compounds of formula (I) wherein A represents a $-CH_2-CH_2-$ group can undergo dehydrogenation in the presence of an optionally supported palladium or platinum catalyst, so as to give rise to the corresponding aromatic derivative wherein A is -CH=CH-, as per (st.34) of the process.

See the experimental section for any specific example concerning the preparation of the compounds of formula (I) of the invention and their conversion into other compounds of formula (I).

The intermediate compounds of formula (Va) or (Vb) according to step (st.3) of the process



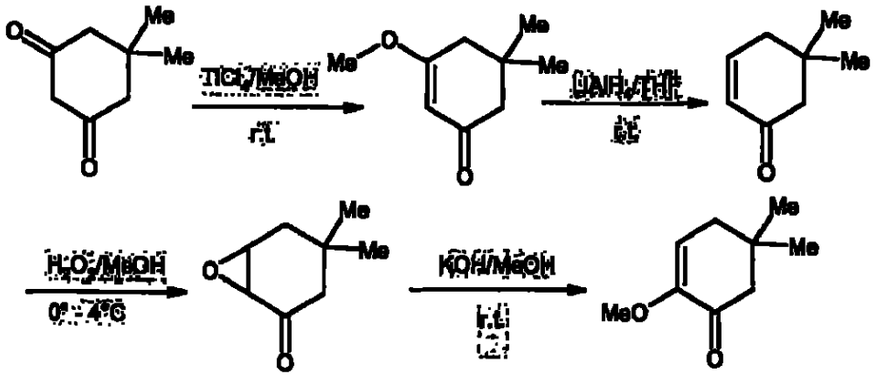
and wherein R_1 is a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl are novel and, hence, represent a further object of the invention.

According to any variant of the process for preparing the compounds of formula (I), the starting material and any other reactant is known or easily prepared according to known methods.

As an example, 2-ethoxy-2-cyclohexen-1-one is a known compound which can be easily obtained by refluxing cyclohexan-1,2-dione with ethanol in toluene, in the presence of catalytic amounts of p-toluenesulfonic acid (TsOH).

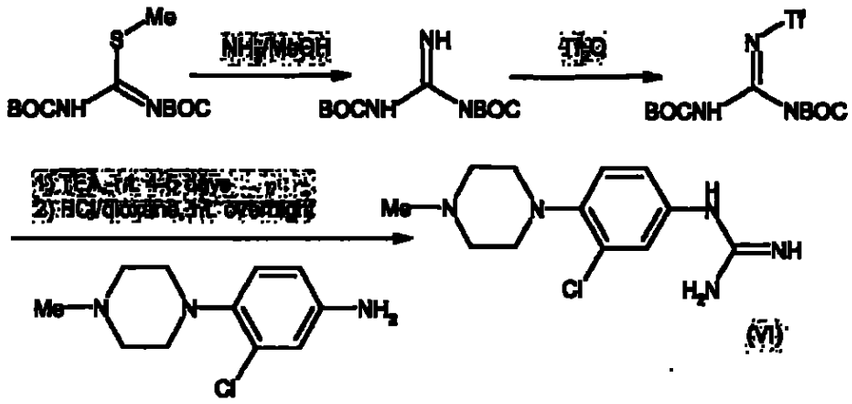
Likewise, 2-methoxy-4,4-dimethyl-2-cyclohexen-1-one is a known compound which can be prepared through epoxidation of commercially available 4,4-dimethyl-2-cyclohexen-1-one and subsequent treatment of the epoxide with potassium hydroxide in methanol.

Finally, 2-methoxy-5,5-dimethyl-2-cyclohexen-1-one may be prepared according to the following scheme from commercially available 5,5-dimethyl-cyclohexan-1,3-dione:



The compounds of formula (III), (VI), (VII), (XVI), (XXII), (XXIII), (XXIV), (XXV), (XXVI), (XXVII), (XXVIII), (XXIX) and (XXX) are known or easily prepared according to known methods.

Just as an example, when preparing given guanidino derivatives of formula (VI) wherein R is a rather complex chemical moiety, the following scheme may be followed:



(VI)

From all of the above, it is clear to the skilled man that when preparing the compounds of formula (I) according to any one of the aforementioned process variants, optional functional groups within the starting materials or the intermediates thereof and which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques. Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

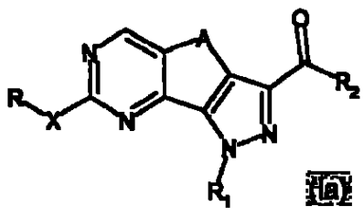
As it will be readily appreciated, if the compounds of formula (I) prepared according to the process described above are obtained as an admixture of isomers, their separation into the single isomers of formula (I), according to conventional techniques, is within the scope of the present invention.

Conventional techniques for racemate resolution include, for instance, partitioned crystallization of diastereoisomeric salt derivatives or preparative chiral HPLC.

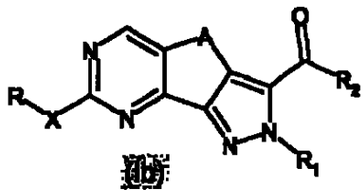
In addition, the compounds of formula (I) of the invention may be also prepared according to combinatorial chemistry techniques widely known in the art, for instance by accomplishing the aforementioned reactions between the several intermediates in a serial manner and by working under solid-phase-synthesis (SPS) conditions.

For a general reference to the preparation of the compounds of formula (I) of the invention according to combinatorial chemistry techniques, see the experimental section.

Hence, it is a further object of the present invention a library of two or more compounds of formula (Ia) or (Ib)



(Ia)



(Ib)

wherein

R is hydrogen or an optionally substituted group selected from amino, straight or branched C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl;

X is a single bond or a divalent radical selected from -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- or $-SO_2-$, wherein R' is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R and R' may form a 5 to 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

R_1, bonded to any one of the nitrogen atoms of the pyrazole ring as per formulae (Ia) or (Ib), represents a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, in formula (Ib), R_1 is a divalent $-(CH_2)_n$-NH- group being linked to R_2, wherein n is 2 or 3;

R_2 is a group selected from -NR"R'", -N(OH)R", -OR" or -R", wherein R" and R'" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R" and R'" may form a 5 to 6 membered heteroaryl or heterocyclyl group, optionally containing one additional heteroatom selected among N, O or S;

A is a divalent group selected from $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ or -CH=CH-;

or a pharmaceutically acceptable salt thereof.

PHARMACOLOGY

The compounds of formula (I) are active as protein kinase inhibitors and are therefore useful, for instance, to restrict the unregulated proliferation of tumor cells.

In therapy, they may be used in the treatment of various tumors, such as those formerly reported, as well as in the treatment of other cell proliferative disorders such as psoriasis, vascular smooth cell proliferation associated with atherosclerosis and post-surgical stenosis and restenosis and in the treatment of Alzheimer's disease.

The inhibiting activity of putative cdk/cyclin inhibitors and the potency of selected compounds is determined through a method of assay based on the use of the SPA technology (Amersham Pharmacia Biotech).

The assay consists of the transfer of radioactivity labelled phosphate moiety by the kinase to a biotinylated substrate. The resulting 33P-labelled biotinylated product is allowed to bind to streptavidin-coated SPA beads (biotin capacity 130 pmol/mg), and light emitted was measured in a scintillation counter.

Inhibition assay of cdk2/Cyclin A activity

Kinase reaction: 4 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 μM ATP (0.1 microCi $P^{33}\gamma$-ATP), 1.1 nM Cyclin A/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 60 min at room temperature, the reaction was stopped by addition of 100 μl PBS buffer containing 32 mM EDTA, 500 μM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: inhibitors were tested at different concentrations ranging from 0.0015 to 10 μM. Experimental data were analyzed by the computer program GraphPad Prizm using the four parameter logistic equation:

y = bottom+(top-bottom)/(1+10^((logIC50-x)*slope))

where x is the logarithm of the inhibitor concentration, y is the response; y starts at bottom and goes to top with a sigmoid shape.

Ki calculation:

Experimental method: Reaction was carried out in buffer (10 mM Tris, pH 7.5, 10 mM $MgCl_2$, 0.2 mg/ml BSA, 7.5 mM DTT) containing 3.7 nM enzyme, histone and ATP (constant ratio of cold/labeled ATP 1/3000). Reaction was stopped with EDTA

and the substrate captured on phosphomembrane (Multiscreen 96 well plates from Millipore). After extensive washing, the multiscreen plates were read on a top counter. Control (time zero) for each ATP and histone concentrations was measured.

Experimental design: Reaction velocities are measured at four ATP, substrate (histone) and inhibitor concentrations. An 80-point concentration matrix was designed around the respective ATP and substrate Km values, and the inhibitor IC50 values (0.3, 1, 3, 9 fold the Km or IC50 values). A preliminary time course experiment in the absence of inhibitor and at the different ATP and substrate concentrations allows the selection of a single endpoint time (10 min) in the linear range of the reaction for the Ki determination experiment.

Kinetic parameter estimates: Kinetic parameters were estimated by simultaneous nonlinear least-square regression using [Eq.1] (competitive inhibitor respect to ATP, random mechanism) using the complete data set (80 points):

$$v=\frac{Vm\bullet A\bullet B}{\alpha\bullet Ka\bullet Kb+\alpha\bullet Ka\bullet B+\alpha\bullet Kb\bullet A+A\bullet B+\alpha\bullet\frac{Ka}{Ki}\bullet I\bullet(Kb+\frac{B}{\beta})} \quad [Eq.1]$$

where A=[ATP], B=[Substrate], I=[inhibitor], Vm= maximum velocity, Ka, Kb, Ki the dissociation constants of ATP, substrate and inhibitor respectively. α and β the cooperativity factor between substrate and ATP binding and substrate and inhibitor binding respectively.

In addition the selected compounds are characterized on a panel of ser/thre kinases strictly related to cell cycle (cdk2/cyclin E, cdk1/cyclin B1, cdk5/p25, cdk4/ cyclin D1), and also for specificity on MAPK, PKA, EGFR, IGF1-R, Aurora-2 and Cdc 7

Inhibition assay of cdk2/Cyclin E activity

Kinase reaction: 10 μM in house biotinylated histone H1 (Sigma # H-5505) substrate, 30 μM ATP (0.3 microCi $P^{33}\gamma$-ATP), 4 ng GST-Cyclin E/CDK2 complex, inhibitor in a final volume of 30 μl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 60 min at room temperature, the reaction was stopped by addition of 100 μl PBS buffer containing 32 mM EDTA, 500 μM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 μL of suspension were

withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above

Inhibition assay of cdk1/Cyclin B1 activity

Kinase reaction: 4 µM in house biotinylated histone H1 (Sigma # H-5505) substrate, 20 µM ATP (0.2 microCi $P^{33}\gamma$-ATP), 3 ng Cyclin B/CDK1 complex, inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After 20 min at r.t. incubation, reaction was stopped by 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, containing 1 mg SPA beads. Then a volume of 110 µl is transferred to Optiplate. After 20 min. incubation for substrate capture, 100 µl 5M CsCl were added to allow statification of beads to the top of the Optiplate and let stand 4 hours before radioactivity counting in the Top-Count instrument.

IC_{50} determination: see above

Inhibition assay of cdk5/p25 activity

The inhibition assay of cdk5/p25 activity is performed according to the following protocol.

Kinase reaction: 10 µM biotinylated histone H1 (Sigma # H-5505) substrate, 30 µM ATP (0.3 microCi $P^{33}\gamma$-ATP), 15 ng CDK5/p25 complex, inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above

Inhibition assay of cdk4/Cyclin D1 activity

Kinase reaction: 0,4 µM mouse GST-Rb (769-921) (# sc-4112 from Santa Cruz) substrate, 10 µM ATP (0.5 µCi $P^{33}\gamma$-ATP), 100 ng of baculovirus expressed GST-

cdk4/GST-Cyclin D1, suitable concentrations of inhibitor in a final volume of 50 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) were added to each well of a 96 U bottom well plate. After 40 min at 37 °C incubation, reaction was stopped by 20 µl EDTA 120 mM.

Capture: 60 µl were transferred from each well to MultiScreen plate, to allow substrate binding to phosphocellulose filter. Plates were then washed 3 times with 150 µl/well PBS Ca^{++}/Mg^{++} free and filtered by MultiScreen filtration system.

Detection: filters were allowed to dry at 37°C, then 100 µl/well scintillant were added and ^{33}P labeled Rb fragment was detected by radioactivity counting in the Top-Count instrument.

IC_{50} determination: see above

<u>Inhibition assay of MAPK activity</u>

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 15 µM ATP (0.15 microCi $P^{33}\gamma$-ATP), 30 ng GST-MAPK (Upstate Biotechnology # 14-173), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above

<u>Inhibition assay of PKA activity</u>

Kinase reaction: 10 µM in house biotinylated histone H1 (Sigma # H-5505) substrate, 10 µM ATP (0.2 microM $P^{33}\gamma$-ATP), 0.45 U PKA (Sigma # 2645), inhibitor in a final volume of 30 µl buffer (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 90 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 µL of suspension were withdrawn and

transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above

Inhibition assay of EGFR activity

Kinase reaction: 10 µM in house biotinylated MBP (Sigma # M-1891) substrate, 2 µM ATP (0.04 microCi $P^{33}\gamma$-ATP), 36 ng insect cell expressed GST-EGFR, inhibitor in a final volume of 30 µl buffer (Hepes 50 mM pH 7.5, $MgCl_2$ 3 mM, $MnCl_2$ 3 mM, DTT 1 mM, $NaVO_3$ 3 µM, + 0.2 mg/ml BSA) were added to each well of a 96 U bottom. After incubation for 20 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above

Inhibition assay of IGF1-R activity

The inhibition assay of IGF1-R activity is performed according to the following protocol.

Enzyme activation: IGF1-R must be activated by auto-phosphorylation before starting the experiment. Just prior to the assay, a concentrated enzyme solution (694 nM) is incubated for half a hour at 28°C in the presence of 100 µM ATP and then brought to the working dilution in the indicated buffer.

Kinase reaction: 10 µM biotinylated IRS1 peptide (PRIMM) substrate, 0-20 µM inhibitor, 6 µM ATP, 1 microCi ^{33}P-ATP, and 6 nM GST-IGF1-R (pre-incubated for 30 min at room temperature with cold 60 µM cold ATP) in a final volume of 30 µl buffer (50 mM HEPES pH 7.9, 3 mM $MnCl_2$, 1 mM DTT, 3 µM $NaVO_3$) were added to each well of a 96 U bottom well plate. After incubation for 35 min at room temperature, the reaction was stopped by addition of 100 µl PBS buffer containing 32 mM EDTA, 500 µM cold ATP, 0.1% Triton X100 and 10mg/ml streptavidin coated SPA beads. After 20 min incubation, 110 µL of suspension were withdrawn and transferred into 96-well

OPTIPLATEs containing 100 µl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

Inhibition assay of Aurora-2 activity

Kinase reaction: 8 µM biotinylated peptide (4 repeats of LRRWSLG), 10 µM ATP (0.5 uCi $P^{33}\gamma$-ATP), 7.5 ng Aurora 2, inhibitor in a final volume of 30 µl buffer (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.2 mg/ml BSA, 3 µM orthovanadate) were added to each well of a 96 U bottom well plate. After 60 minutes at room temperature incubation, reaction was stopped and biotinylated peptide captured by adding 100 µl of bead suspension.

Stratification: 100 µl of CsCl2 5 M were added to each well and let stand 4 hour before radioactivity was counted in the Top-Count instrument.

IC_{50} determination: see above

Inhibition assay of Cdc7/dbf4 activity

The inhibition assay of Cdc7/dbf4 activity is performed according to the following protocol.

The Biotin-MCM2 substrate is trans-phosphorylated by the Cdc7/Dbf4 complex in the presence of ATP traced with γ^{33}-ATP. The phosphorylated Biotin-MCM2 substrate is then captured by Streptavidin-coated SPA beads and the extent of phosphorylation evaluated by β counting.

The inhibition assay of Cdc7/dbf4 activity was performed in 96 wells plate according to the following protocol.

To each well of the plate were added:

- 10 µl substrate (biotinylated MCM2, 6 µM final concentration)
- 10 µl enzyme (Cdc7/Dbf4, 17.9 nM final concentration)
- 10 µl test compound (12 increasing concentrations in the nM to µM range to generate a dose-response curve)
- 10 µl of a mixture of cold ATP (2 µM final concentration) and radioactive ATP (1/5000 molar ratio with cold ATP) was then used to start the reaction which was allowed to take place at 37°C.

Substrate, enzyme and ATP were diluted in 50 mM HEPES pH 7.9 containing 15 mM $MgCl_2$, 2 mM DTT, 3 μM $NaVO_3$, 2mM glycerophosphate and 0.2mg/ml BSA. The solvent for test compounds also contained 10% DMSO.

After incubation for 60 minutes, the reaction was stopped by adding to each well 100 μl of PBS pH 7.4 containing 50 mM EDTA, 1 mM cold ATP, 0.1% Triton X100 and 10 mg/ml streptavidin coated SPA beads.

After 20 min incubation, 110 μL of suspension were withdrawn and transferred into 96-well OPTIPLATEs containing 100 μl of 5M CsCl. After 4 hours, the plates were read for 2 min in a Packard TOP-Count radioactivity reader.

IC_{50} determination: see above.

The compounds of the present invention can be administered either as single agents or, alternatively, in combination with known anticancer treatments such as radiation therapy or chemotherapy regimen in combination with cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, and the like.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g., to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, conditions of the patient and administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 500 mg per dose, from 1 to 5 times daily. The compounds of the invention can be administered in a variety of dosage forms, e.g.,

orally, in the form tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form suppositories; parenterally, e.g., intramuscularly, or through intravenous and/or intrathecal and/or intraspinal injection or infusion.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient, which may be a carrier or a diluent.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a suitable pharmaceutical form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g., silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g., starches, arabic gum, gelatine methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g., starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tabletting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g., syrups, emulsions and suspensions.

As an example, the syrups may contain, as carrier, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain, as examples of carriers, natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., sterile water, olive oil, ethyl oleate, glycols, e.g., propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain, as a carrier, sterile water or preferably they may be in the form of sterile, aqueous, isotonic, saline solutions or they may contain propylene glycol as a carrier.

The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g., cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

With the aim to better illustrate the present invention, without posing any limitation to it, the following examples are now given.

EXAMPLES

Several compounds of formula (I), hence including those of formula (Ia) and (Ib) of the invention, have been prepared. Whilst some of them have been specifically named and listed in the following experimental section, most have been conveniently identified as per the coding system of the tables reported in the experimental section, together with their analytical data.

Each code, which unambiguously identifies a single specific compound of formula (I) only, consists of five units B-X-M(C)-D.

Code B represents any R substituent, as per formula (I), being attached to the rest of the molecule through the X linkage; each B group is represented through the proper chemical formula in the following table I, also indicating its point of attachment to the rest of the molecule X-M.

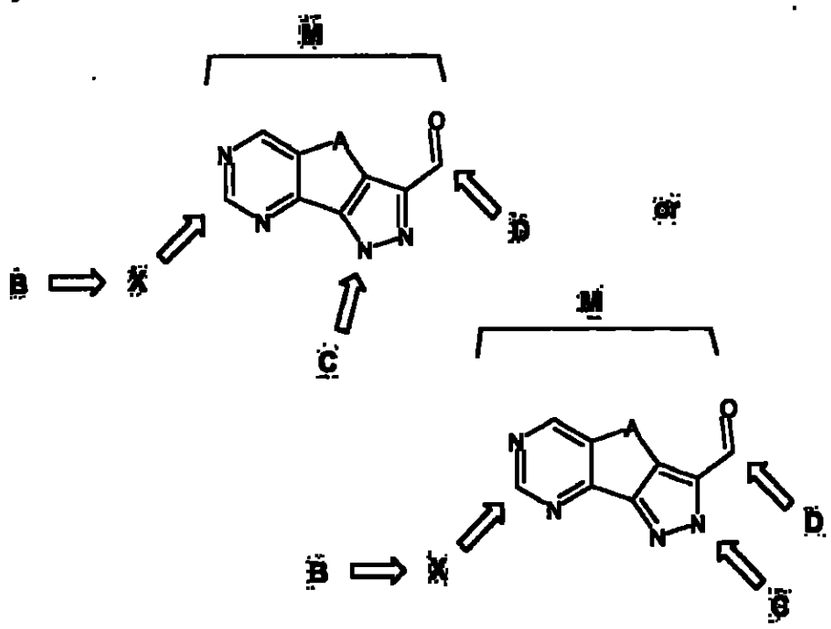
Code X just represents the X group in formula (I); its meanings are represented in the following table II, also indicating its point of attachment to the rest of the molecule M.

Code C represents the R_1 group being attached to the rest of the molecule through any one of the pyrazole nitrogen atoms, as per formula (I). Each C group is represented through the proper chemical formula in the following table III, also indicating its point of attachment to the rest of the molecule M.

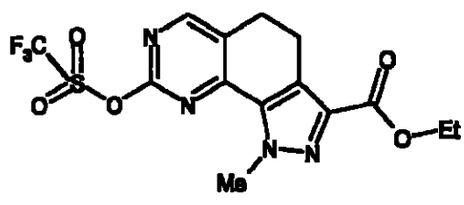
Code D represents the R_2 group being attached to the rest of the molecule through the carbonyl group, as per formula (I). Each D group is represented through the proper chemical formula in the following table IV, also indicating its point of attachment to the rest of the molecule M.

Finally, code M refers to the central core of the molecule (I) bearing a carbonyl group in position 3. From all of the above it is clear to the skilled person that M is substituted by groups -X- (code X), R_1 (code C) and R_2 (code D), as reported in formula (I); each M group is represented through the proper chemical formula, in table V, also indicating the positions of the other substituents.

Therefore, the coding system presently used for some compounds of formula (I) can be shortly summarised as follows:



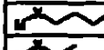
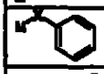
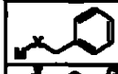
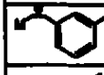
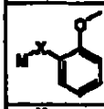
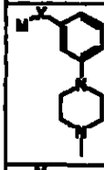
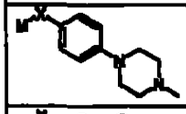
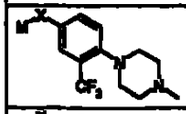
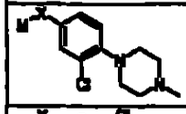
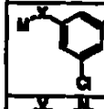
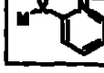
Just as an example, which is not intended to limit the scope of the present invention, the compound B66-X03-M00(C01)-D01 (see example 36) represents the pyrazolo-quinazoline derivative of formula (Ia) wherein the central core is represented by the moiety M00 of table V, R is the group of formula B66 of table I, X is the divalent group X03 of table II, R_1 is the group C01 of table III and R_2 is the group D01 of table IV, having formula

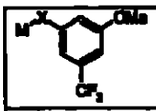
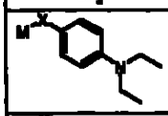
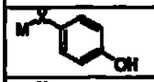
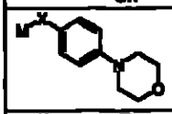
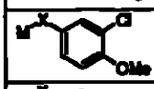
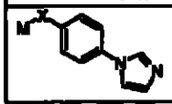
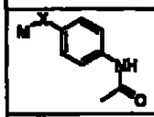
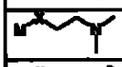
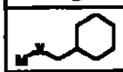
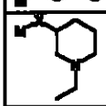
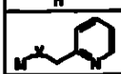
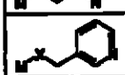
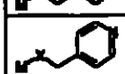
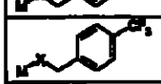
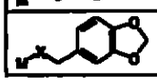


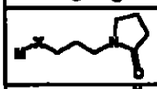
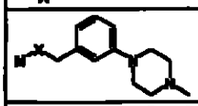
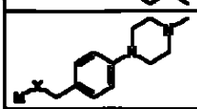
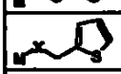
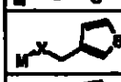
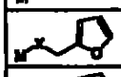
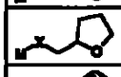
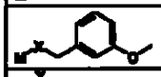
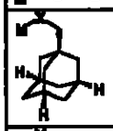
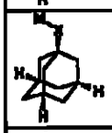
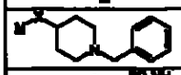
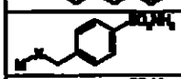
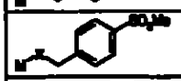
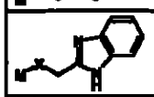
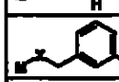
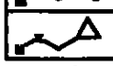
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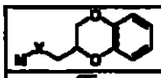
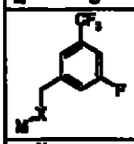
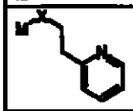
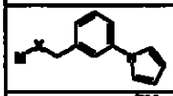
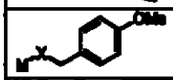
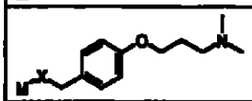
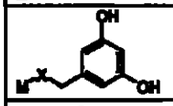
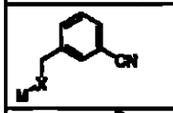
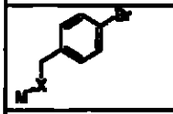
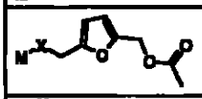
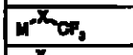
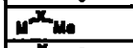
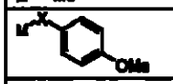
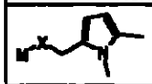
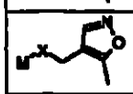
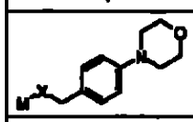
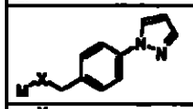
From all of the above, it is clear to the skilled person that when R_1 and R_2 are linked together as per formula (Ib), then this additional cycle is already included in the structure of the M moiety and, hence, codes C and D are missing.

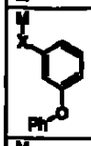
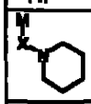
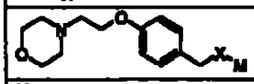
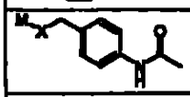
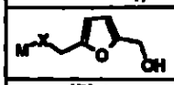
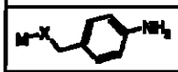
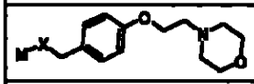
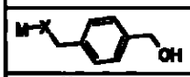
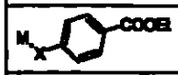
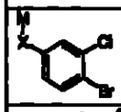
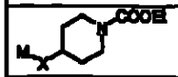
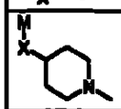
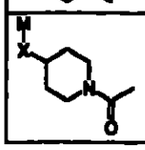
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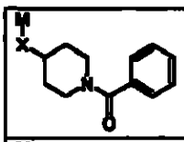
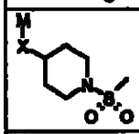
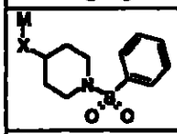
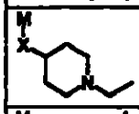
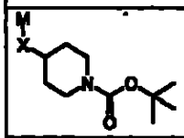
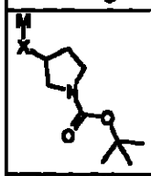
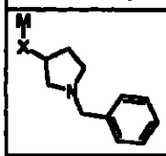
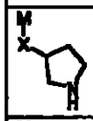
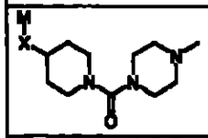
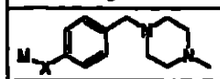
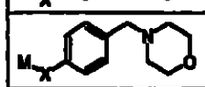
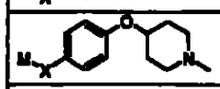
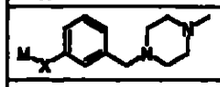
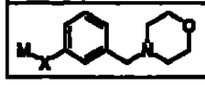
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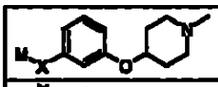
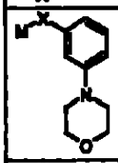
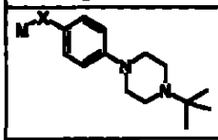
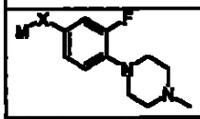
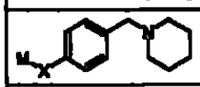
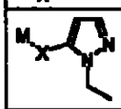
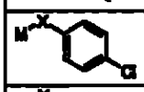
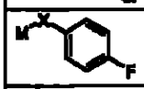
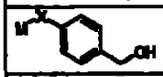
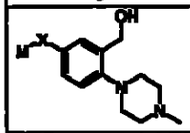
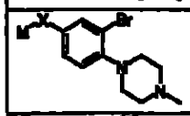
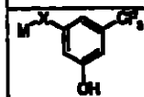
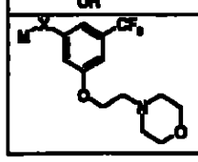
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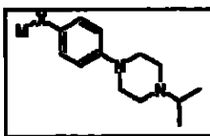
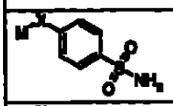
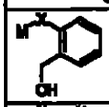
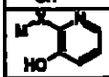
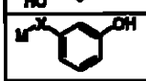
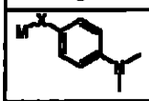
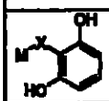
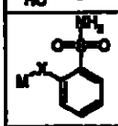
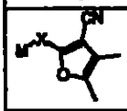
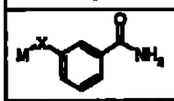
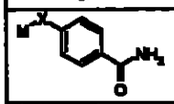
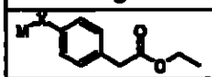
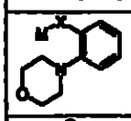
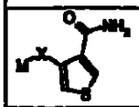
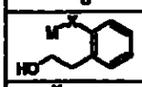
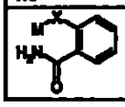
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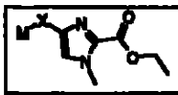
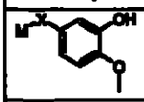
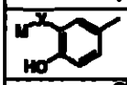
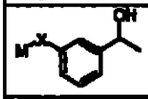
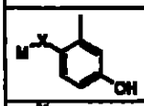
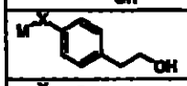
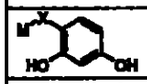
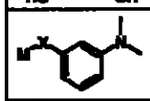
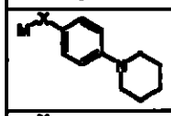
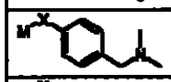
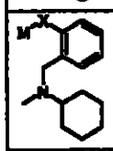
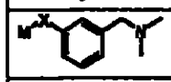
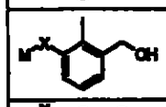
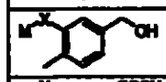
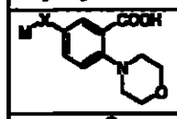
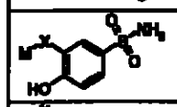
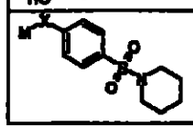
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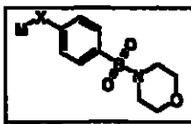
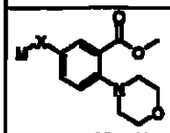
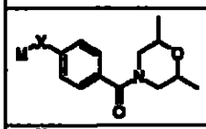
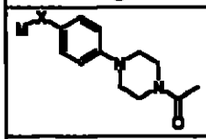
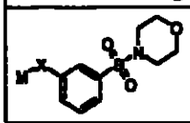
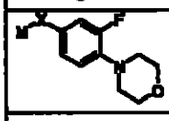
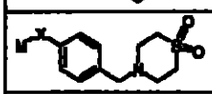
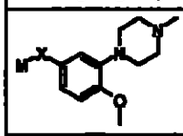
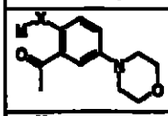
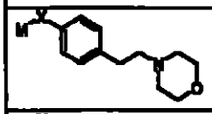
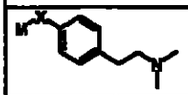
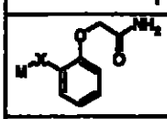
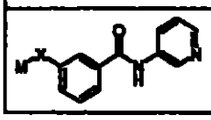
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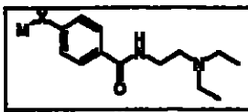
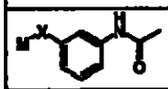
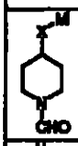
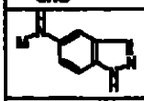
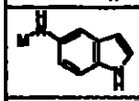
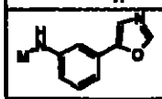
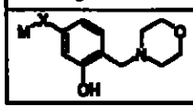
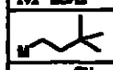
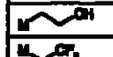
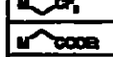
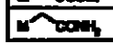
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Table II

TABLE OF X LINKERS	
Fragment	Code
-NH-M	X00
-CONH-M	X01
-NHCONH-M	X02
-O-M	X03
-S-M	X04
$-SO_2-M$	X05
-M	X06

Table III

TABLE OF C GROUPS	
Fragment	Code
M-H	C00
M-Me	C01
M-tBu	C02
	C03
	C04
	C05
	C06
	C07

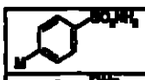
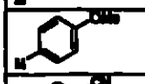
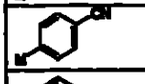
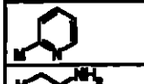
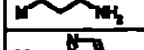
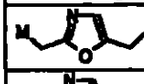
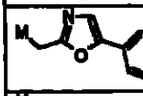
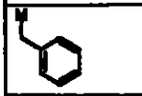
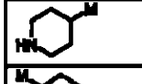
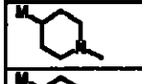
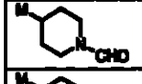
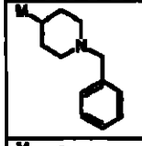
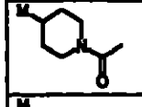
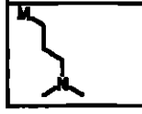
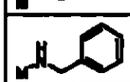
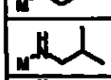
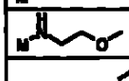
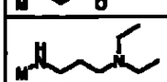
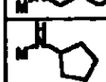
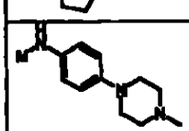
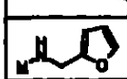
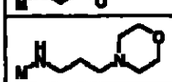
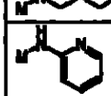
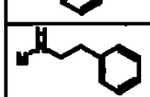
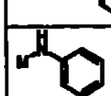
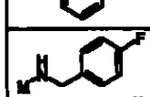
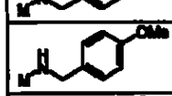
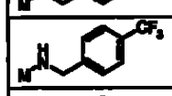
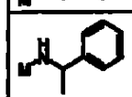
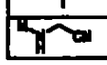
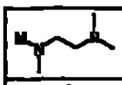
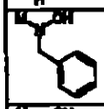
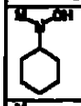
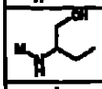
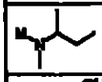
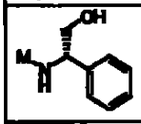
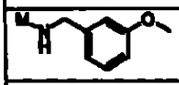
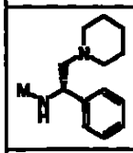
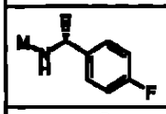
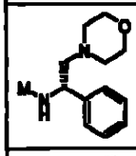
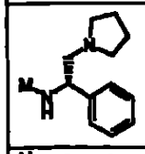
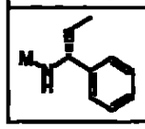
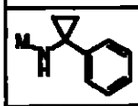
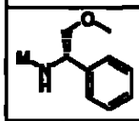
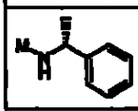
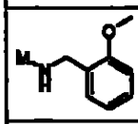
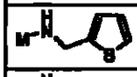
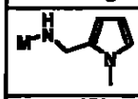
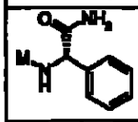
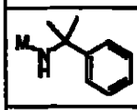
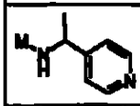
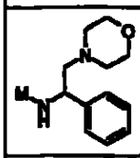
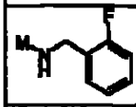
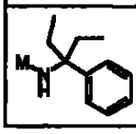
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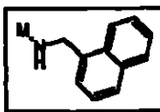
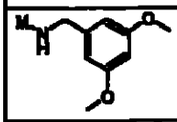
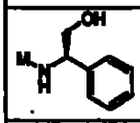
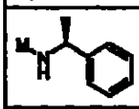
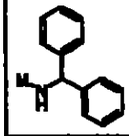
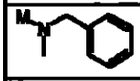
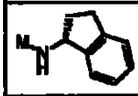
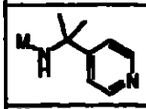
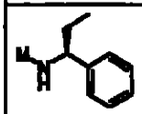
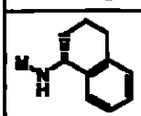
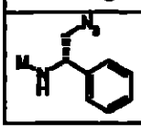
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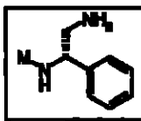
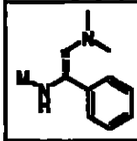
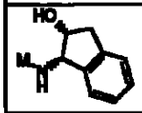
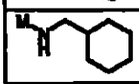
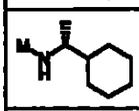
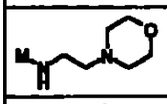
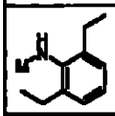
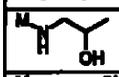
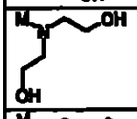
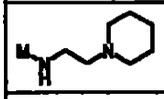
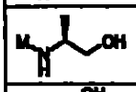
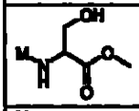
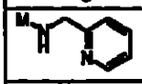
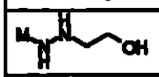
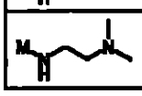
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M-OH	D02

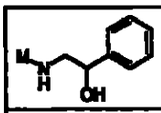
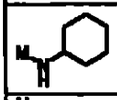
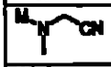
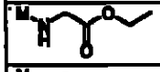
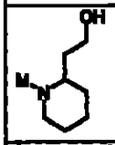
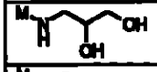
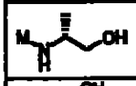
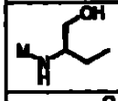
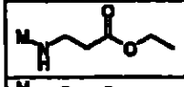
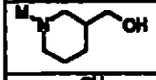
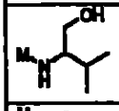
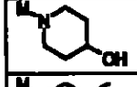
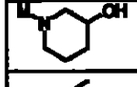
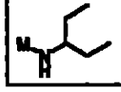
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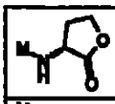
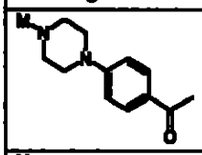
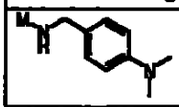
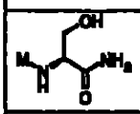
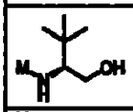
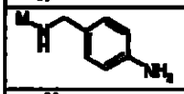
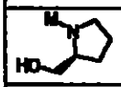
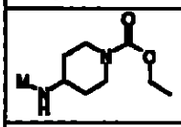
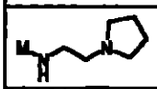
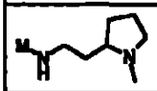
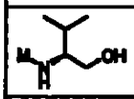
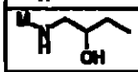
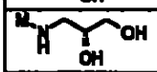
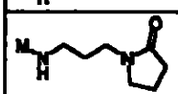
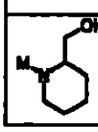
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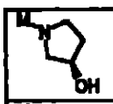
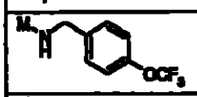
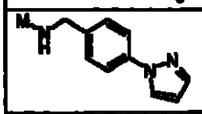
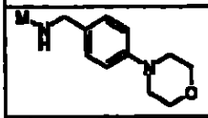
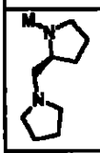
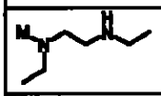
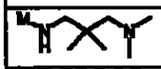
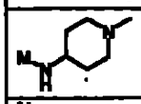
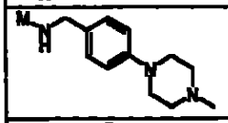
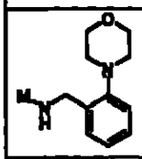
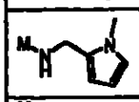
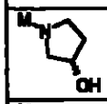
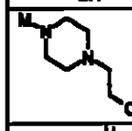
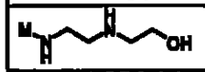
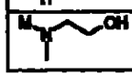
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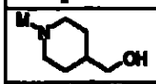
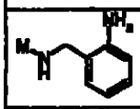
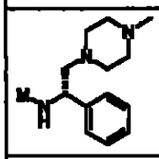
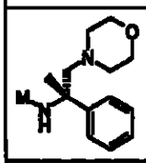
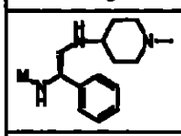
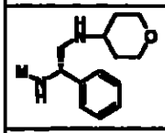
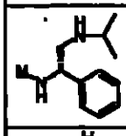
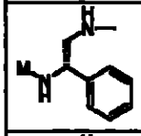
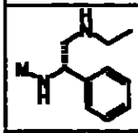
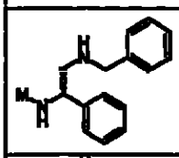
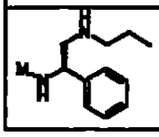
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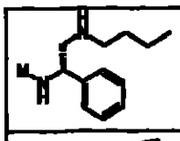
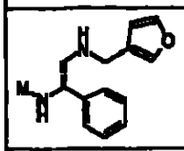
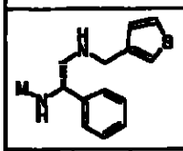
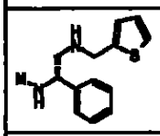
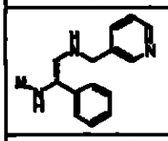
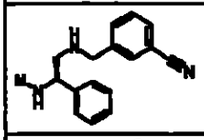
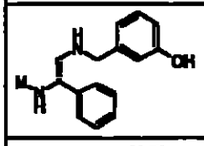
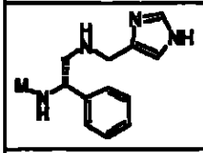
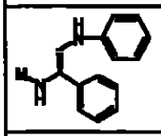
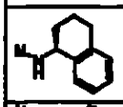
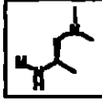
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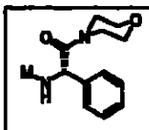
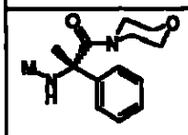
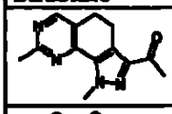
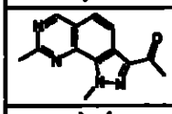
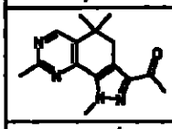
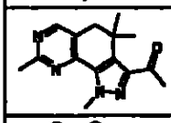
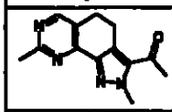
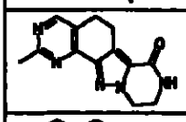
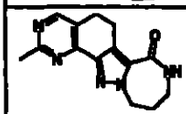
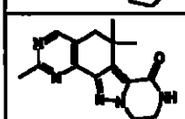
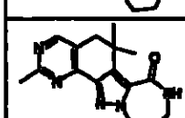
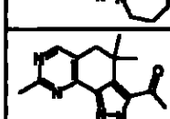
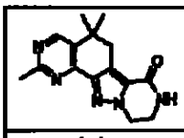
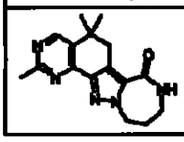
	D164
	D165

Table V

TABLE OF M CORE	
Structure	Code
	M00
	M01
	M02
	M03
	M04
	M05
	M06
	M07
	M08
	M09

	M10
	M11

The compounds of the present invention, as prepared according to the following examples, were also characterized by ^{1}H NMR and/or by HPLC/MS analytical data; HPLC/MS data were collected following any one of methods 1, 2 or 3.

HPLC/MS Method 1

The HPLC equipment consisted of a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Instrument control, data acquisition and data processing were provided by Empower and MassLynx 4.0 software.

HPLC was carried out at 25°C at a flow rate of 1 mL/min using a RP18 Waters X Terra (4,6 x 50 mm, 3.5 µm) column. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and Mobile phase B was H_2O/acetonitrile (5:95); the gradient was from 10 to 90% B in 8 minutes then hold 90% B 2 minutes. The injection volume was 10 µl.

The mass spectrometer was operated in positive and in negative ion mode, the capillary voltage was set up at 2.5 KV; the source temperature was 120°C; cone was 10 V; full scan, mass range from 100 to 800 amu was set up.

HPLC/MS Method 2

The HPLC equipment consisted of a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Instrument control, data acquisition and data processing were provided by Empower and MassLynx 4.0 software.

HPLC was carried out at 25 °C at a flow rate of 1 mL/min using a RP18 Waters X Terra (3.0 x 30 mm, 3.5 µm) column. Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid/acetonitrile 95:5), and Mobile phase B was H_2O/acetonitrile (5:95); the gradient was from 10 to 90% B in 4 min then hold 90% B 1 minute. The injection volume was 10 µl.

The mass spectrometer was operated in positive and in negative ion mode, the capillary voltage was set up at 2.5 KV; the source temperature was 120°C; cone was 10 V; full scan, mass range from 100 to 800 amu was set up.

HPLC/MS Method 3

Mass spectra were recorded on a Finnigan LCQ ion trap mass spectrometer using the electrospray (ESI) ionization technique with positive and negative ion detection. The mass spectrometer is directly connected to a SSP4000 HPLC system (Thermo Separation), equipped with an LcPal autosampler (CTC Analytics) and a UV 6000LP PDA detector (Thermo Separation). Instrument control, data acquisition and processing were performed by using Xcalibur 1.2 software. HPLC analysis were carried out at room temperature at a flow rate of 1 mL/min using an RP C18 Waters ZorbaxSB C18 column (4.6x 50mm; 1.8 μm).

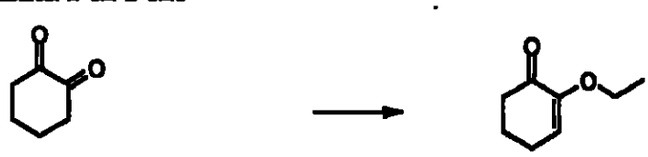
Mobile phase A was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid): acetonitrile 90:10, and Mobile phase B was ammonium acetate 5 mM buffer (pH 5.5 with acetic acid): acetonitrile 10:90; the gradient was from 0 to 100% B in 7 minutes then hold 100% B for 2 minutes before requilibration. Total LC time is 12 minutes. The injection volume was 10μl. UV Detection was performed between 215 and 400 nm.

Ions were generated under the following conditions: ESI sprayer voltage 4.0 kV, heated capillary temperature 255°C, sheath gas nitrogen with a pressure of 5.0 Bar. A full scan detection mode (from 50 to 1000 amu) was used with an MS/MS analysis of the most intense ion (normalized collision energy: 35%).

UV Detection: 215-400 nm.

Example 1

2-ethoxycyclohex-2-en-1-one



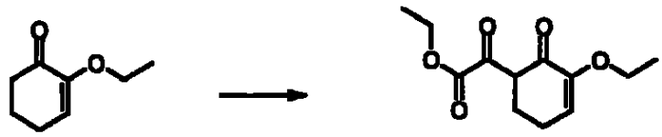
50 g (0.45 mol) of 1,2-dicyclohexandione were dissolved in a mixture of 1 L of toluene and 0.5 L of ethanol. 10 g of p-toluenesulfonic acid were added and the solution heated at reflux for 2 days. (TLC chloroform/methanol 6/1). The solvent was then evaporated, the residue redissolved with dichloromethane and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated. The crude was

purified by chromatography on a silica gel column by eluting with a mixture of cyclohexane/ethyl acetate 98/2 (66 % yield as an oil).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, 3 H) 2.33-2.39 (m, 6 H) 3.67 (q, 2 H) 5.97 (t, 1 H).

Example 2

Ethyl (3-ethoxy-2-oxocyclohex-3-en-1-yl)(oxo)acetate



41.40 g (0.29 mol) of 2-ethoxycyclohex-2-en-1-one were dissolved in 310 mL of diethyl ether and 325 mL of 1M $LiN(TMS)_2$ in tetrahydrofuran were added dropwise at −50°C. After 30 minutes at the same temperature, 44.2 mL of diethyloxalate were also added under stirring. The solution was kept at room temperature overnight (TLC chloroform). 300 mL of water were then added, the pH adjusted to 4-5 by adding 1 N HCl and the resulting solution extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude was purified by chromatography on a silica gel column eluted by chloroform (76 % yield as an oil).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H) 1.51 (t, 3 H) 2.06-2.58 (m, 4 H) 3.57 (m, 1 H) 3.86 (q, 2 H) 4.38 (q, 2 H) 6.09 (m, 1 H).

Example 3

Ethyl 1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



30 g (0.125 mol) of ethyl (3-ethoxy-2-oxocyclohex-3-en-1-yl)(oxo)acetate were dissolved in 150 mL of glacial acetic acid and 6.5 mL of methylhydrazine were added. The mixture was stirred at room temperature for 6 hours. The solvent was then evaporated and the crude redissolved with water, the solution made basic with 30 % NH_4OH and extracted with chloroform. The organic layer was then dried over Na_2SO_4 and concentrated. The residue was chromatographed on a silica gel column (eluant:

chloroform) and crystallized from a mixture n-hexane/diethyl ether (TLC chloroform; 63 % yield as a white solid).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J* 6.89 Hz, 3 H) 1.51 (t, *J* 6.94 Hz, 3 H) 2.06-2.58 (m, 4 H) 3.57 (m, 1 H) 3.86 (q, *J* 6.83 Hz, 2 H) 4.38 (q, *J* 6.94 Hz, 2 H; 6.09 (m, 1 H).

According to the same method, but employing the suitable substituted hydrazine derivative, the following compounds were prepared:

ethyl 1-tert-butyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J* 6.83 Hz, 3 H) 1.58 (s, 9 H) 2.30-2.93 (3m, 6 H) 4.18 (q, *J* 6.83 Hz, 2 H);

ethyl 1-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.3 (t, *J* 7.20 Hz, 3 H) 1.9-2.9 (3m, 6 H) 3.7 (m, 2 H) 4.3 (q, *J* 7.20 Hz, 2 H) 4.53 (t, *J* 5.85, 2 H) 4.77 (t, *J* 5.73, OH);

ethyl 1-(2-ethoxy-2-oxoethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.18 (t, *J* 7.20 Hz, 3 H) 1.29 (t, *J* 7.20 Hz, 3 H) 2.04 (m, 2 H); 2.52 (m, 2 H) 2.93 (t, *J* 6.10 Hz, 2 H) 4.04 (q, *J* 7.07 Hz, 2 H) 4.37 (q, *J* 7.20 Hz, 2 H) 5.26 (s, 1 H);

ethyl 7-oxo-1-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 2.05 (m, 2 H) 2.57 (m, 2 H) 2.95 (m, 2 H) 4.2 (q, *J* 7.07 Hz, 2 H) 5.3 (2d, 2 H);

ethyl 7-oxo-2-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.08 Hz, 3 H) 2.05 (m, 2 H) 2.57 (t, J 7.44 Hz, 2 H) 2.94 (m, 2 H) 4.30 (q, J 7.19 Hz, 2 H) 5.46 (2d, 2 H);

ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J*=7.07 Hz, 3 H) 2.04 (m, 2 H) 2.51 (m, 2 H) 2.87 (t, *J*=6.10 Hz, 2 H) 4.27 (q, *J*=7.11 Hz, 2 H) 14.39 (s, 1 H);

ethyl 1-[4-(aminosulfonyl)phenyl]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.13 Hz, 3 H) 2.10 - 2.19 (m, 2 H) 2.57 - 2.63 (m, 2 H) 3.05 (t, *J*=6.10 Hz, 2 H) 4.37 (q, *J*=7.07 Hz, 2 H) 7.54 (s, 2 H) 7.77 (d, *J*=8.78 Hz, 2 H) 7.96 (d, *J*=8.90 Hz, 2 H);

ethyl 1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 2.05 - 2.17 (m, 2 H) 2.56 (dd, *J*=7.26, 5.55 Hz, 2 H) 3.03 (t, *J*=6.10 Hz, 2 H) 3.85 (s, 3 H) 4.34 (q, *J*=7.07 Hz, 2 H) 7.05 (d, *J*=9.02 Hz, 2 H) 7.44 (d, *J*=9.02 Hz, 2 H);

ethyl 1-(4-cyanophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.07 Hz, 3 H) 2.09 - 2.19 (m, 2 H) 2.60 (dd, *J*=7.32, 5.49 Hz, 2 H) 3.04 (t, *J*=6.16 Hz, 2 H) 4.36 (q, *J*=7.11 Hz, 2 H) 7.80 (d, *J*=8.90 Hz, 2 H) 8.03 (d, *J*=8.78 Hz, 2 H);

ethyl 7-oxo-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.13 Hz, 3 H) 2.10 - 2.21 (m, 2 H) 2.58 (dd, *J*=7.32, 5.61 Hz, 2 H) 3.05 (t, *J*=6.16 Hz, 2 H) 4.36 (q, *J*=7.07 Hz, 2 H) 7.61 (ddd, *J*=7.41, 4.73, 1.04 Hz, 1 H) 7.64 (dt, *J*=7.93, 0.98 Hz, 1 H) 8.07 (td, *J*=7.74, 1.83 Hz, 1 H) 8.57 (ddd, *J*=4.79, 1.86, 0.79 Hz, 1 H);

ethyl 7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, 3 H, J 7.08) 2.08 (m, 2 H) 2.54 (m, 2 H) 4.30 (q, 2 H, J 7.08) 7.49 (m, 5 H);

ethyl 1-benzyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 1-(1-methylpiperidin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.84 - 2.11 (m, 6 H) 2.28 (s, 3 H) 2.48 - 2.53 (m, 2 H) 2.52 - 2.60 (m, 2 H) 2.91 - 3.00 (m, 2 H) 2.94 (t, *J*=6.16 Hz, 2 H) 4.32 (q, *J*=7.15 Hz, 2 H) 4.93 - 5.11 (m, 1 H)

(The hydrazino derivative being employed was not commercially available (CAS n° 53242-78-7) and was thus synthetized as described in the literature: WO 02/085906).

ethyl 7-oxo-1-piperidin-4-yl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

(The hydrazino derivative being employed was not commercially available and was thus synthetized as described in the literature: DE 3634942 A1).

ethyl 1-(1-benzylpiperidin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.07 Hz) 3.34 (s, 2 H) 4.31 (q, 2 H, J 7.07 Hz) 5.06 (m, 1 H) 7.35 (m, 5 H);

ethyl 1-(1-acetylpiperidin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

(The hydrazino derivative being employed was not commercially available and was thus synthetized as reported in example 69).

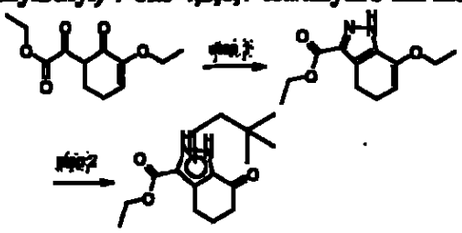
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (bs, 3H) 2.59 (m, 1H) 2.71 (m, 1H) 2.95 (m, 1H) 3.29 (m, 1H) 3.94 (m, 1H) 4.30 (m, 2H) 4.48 (m, 1H) 5.29 (m, 1H)

ethyl 1-(2-dimethylaminoethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 1-(2-dimethylaminopropyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

Example 4

Ethyl 1(2)-(3,3-dimethylbutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



Step 1. Ethyl 7-ethoxy-4,5-dihydro-1 H-indazole-3-carboxylate

1.2 g (5 mmol) of ethyl (3-ethoxy-2-oxocyclohex-3-en-1-yl)(oxo)acetate were dissolved in 20 mL of ethanol and 25 mL (5.2 mmol) of hydrazine hydrate 98% were added dropwise. The solution was stirred at room temperature for 5 hours, then heated at 60°C for further 5 hours. The solvent was removed in vacuo and the residue taken up with diethyl ether and the resulting precipitate collected by filtration giving 0.8 g of the title compound, that was employed in the next step without any further purification.

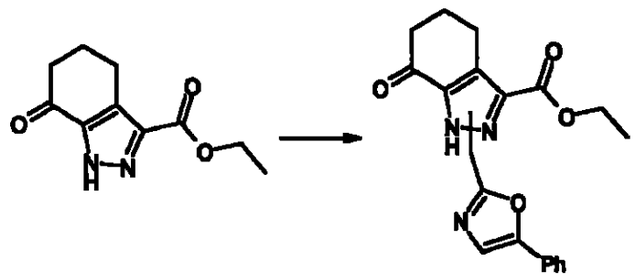
Step 2. Ethyl 1(2)-(3,3-dimethylbutyl)-7-oxo-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate

0.28 g (1.17 mmol) of ethyl 7-ethoxy-4,5-dihydro-1H-indazole-3-carboxylate were dissolved in 12 mL of dry dimethylformamide and 0.25 g (1.40 mmol) of 3,3-dimethylbutyl methanesulfonate were added. The resulting solution was treated with 0.06 g (1.40 mmol) of sodium hydride 60% in mineral oil and the reaction mixture stirred at 65°C for 4 hours. Water was added to the reaction and the solution extracted with ethyl acetate. The solvent was evaporated in vacuo and the residue redissolved with 10 mL of methanol. Few drops of 1 N HCl were then added and after 3 hours the

reaction was partitioned between water and ethyl acetate, giving a crude that, after drying over Na_2SO_4, was purified by chromatography on a silica gel column (eluant hexane/ethyl acetate 95/5) (75% yield).

Example 5

Ethyl 7-oxo-1(2)-[(5-phenyl-1,3-oxazol-2-yl)methyl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



900 mg (4.3 mmol) of ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 26 mL of DMF and 712 mg (5.16 mmol) of K_2CO_3 and 995 mg (5.16 mmol) of 2-(chloromethyl)-5-phenyl-1,3-oxazole were added. The reaction mixture was stirred at room temperature for 5 hours then the solvent was removed under vacuo and the residue was dissolved in dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. By chromatography, 405 mg (30 % yield) of the two regioisomers were recovered.

ethyl 7-oxo-1-[(5-phenyl-1,3-oxazol-2-yl)methyl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

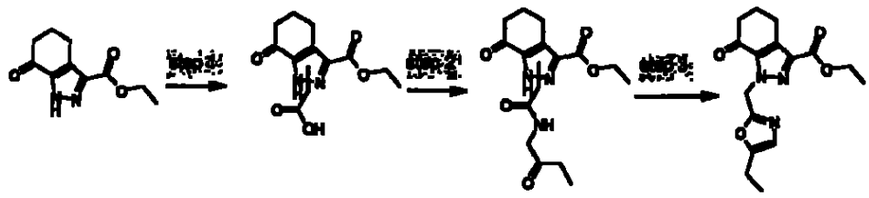
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, 3 H) 2.09 (m, 2 H) 2.59 (m, 2 H) 2.97 (m, 2 H) 4.31 (q, 2 H) 6.04 (s, 2 H) 7.39 (m, 1 H) 7.49 (m, 2 H) 7.63 (s, 1 H) 7.66 (m, 2 H)

ethyl 7-oxo-2-[(5-phenyl-1,3-oxazol-2-yl)methyl]-4,5,6,7-tetrahydro-2H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.09 (m, 2 H) 2.60 (m, 2 H) 2.99 (m, 2 H) 4.31 (q, 2 H) 5.98 (s, 2 H) 7.39 (m, 1 H) 7.49 (m, 2 H) 7.62 (s, 1 H) 7.66 (m, 2 H).

Example 6

Ethyl 1-[(5-ethyl-1,3-oxazol-2-yl)methyl]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



Step 1. [3-(ethoxycarbonyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1(2)-yl]acetic acid

1 g (4.8 mmol) of ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 30 mL of dry DMF and treated with 1.59 g (11.52 mmol) of K_2CO_3 and 800 mg (5.76 mmol) of bromoacetic acid at room temperature. After heating at 80 °C overnight the mixture was cooled and the solvent was removed under vacuo. The crude was dissolved in water and neutralized with HCl 37%. Three extractions with dichloromethane afforded 1.7 g of crude that was purified by flash chromatography (eluant dichloromethane) yielding 783 mg (61 %) of the product as mixture of regioisomers.

Step 2. Ethyl 7-oxo-1(2)-{2-oxo-2-[(2-oxobutyl)amino]ethyl}-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

743 mg (2.79 mmol) of [3-(ethoxycarbonyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1(2)-yl]acetic acid as mixture of isomers were dissolved in 28 mL of DMF and 2.18 g (4.18 mmol) of benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP), 690 mg (5.58 mmol) of 1-aminobutan-2-one hydrochloride and 2.4 mL (13.95 mmol) of N-ethyl-N,N-diisopropylamine were added. After 2 hours the solvent was evaporated under vacuo, the crude was dissolved in dichloromethane and washed with saturated $NaHCO_3$, brine and water. Purification by flash chromatography (eluant hexane/ethylacetate 8/2) yielded 511 mg of ethyl 7-oxo-1-{2-oxo-2-[(2-oxobutyl)amino]ethyl}-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate and 20 mg of ethyl 7-oxo-2-{2-oxo-2-[(2-oxobutyl)amino]ethyl}-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (57 % overall yield).

ethyl 7-oxo-1-{2-oxo-2-[(2-oxobutyl)amino]ethyl}-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 (t, 3 H) 1.32 (t, 3 H) 2.09 (m, 2 H) 2.44 (q, 2 H) 2.52 (t, 2 H) 2.96 (t, 2 H) 3.98 (d, 2 H) 4.31 (q, 2 H) 5.26 (s, 2 H) 8.44 (t, 1 H);

ethyl 7-oxo-2-[2-oxo-2-[(2-oxobutyl)amino]ethyl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 (t, 3 H) 1.31 (t, 3 H) 2.08 (m, 2 H) 2.44 (q, 2 H) 2.53 (t, 2 H) 2.94 (t, 2 H) 3.99 (d, 2 H) 4.29 (q, 2 H) 5.32 (s, 2 H) 8.48 (t, 1 H).

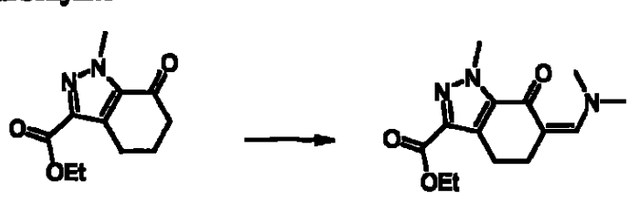
Step 3. Ethyl 1-[(5-ethyl-1,3-oxazol-2-yl)methyl]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

A solution of 506 mg (1.51 mmol) of ethyl 7-oxo-1-{2-oxo-2-[(2-oxobutyl)amino]ethyl}-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate in toluene (45 mL) was treated with 0.422 mL (4.53 mmol) of phosphoric trichloride and heated at 90 °C for 15 hours. The mixture was cooled to room temperature, poured into ice and neutralized with NaOH 5N. The aqueous phase was extracted with dichloromethane and the organic layer afforded 425 mg of crude that was purified on silica gel (eluant hexane/ethylacetate 7/3). 285 mg of the title compound were thus isolated (60 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, 3 H) 1.32 (t, 3 H) 2.08 (m, 2 H) 2.63 (m, 4 H) 2.97 (t, 2 H) 4.31 (q, 2 H) 5.84 (s, 2 H) 6.79 (s, 1 H).

Example 7

Ethyl 6-[(dimethylamino)methylene]-1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



16 g (0.07 mol) of ethyl 1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 100 mL of dimethylformamide and 32 mL of dimethylformamide diterbutyl acetale were added. The mixture was stirred at 60°C for 8 hours. The solvent was then evaporated in vacuo and the product crystallized from ethanol (90 % yield).

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.72-2.95 (m, 4 H) 3.04-3.14 (m, 6 H) 4.10 (s, 3 H) 4.24 (q, *J* 7.20 Hz, 2 H) 7.46 (m, 1 H).

By working according to the same method the following compounds were prepared:

Ethyl 1-tert-butyl-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate;

ethyl 6-[(dimethylamino)methylene]-1-(2-hydroxyethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.80 (t, *J* 6.34 Hz, 2 H) 2.88 (t, *J* 6.21, 2 H) 3.70 (m, 2 H) 4.24 (q, *J* 7.07 Hz, 3 H) 4.58 (t, *J* 5.97 Hz, 2 H) 4.79 (bs, OH) 7.47 (bs, 1 H);

ethyl 6-[(dimethylamino)methylene]-1-(2-ethoxy-2-oxoethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J* 7.07 Hz, 3 H) 1.28 (t, *J* 7.13 Hz, 3 H) 2.86 (m, 4 H) 3.10 (s, 6 H) 4.10 (q, *J* 7.11 Hz, 2 H) 4.26 (q, *J* 7.11 Hz, 2 H) 5.33 (s, 2 H) 7.43 (s, 1 H);

ethyl 1-[4-(aminosulfonyl)phenyl]-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate;

ethyl-6-[(dimethylamino)methylene]-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 2.87 - 2.93 (m, 2 H) 2.95 - 3.00 (m, 2 H) 3.12 (s, 6 H) 3.83 (s, 3 H) 4.32 (q, *J*=7.07 Hz, 2 H) 7.00 (d, *J*=9.02 Hz, 2 H) 7.39 (d, *J*=9.02 Hz, 2 H) 7.42 (s, 1 H);

ethyl 1-(4-cyanophenyl)-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.13 Hz, 3 H) 2.88 - 2.94 (m, 2 H) 2.97 - 3.03 (m, 2 H) 3.14 (s, 6 H) 4.34 (q, *J*=7.15 Hz, 2 H) 7.48 (s, 1 H) 7.73 (d, *J*=8.90 Hz, 2 H) 7.96 (d, *J*=8.78 Hz, 2 H);

ethyl 6-[(dimethylamino)methylene]-7-oxo-1-pyridin-2-yl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 2.87 - 2.93 (m, 2 H) 3.00 (t, *J*=6.71 Hz, 2 H) 3.13 (s, 6 H) 4.33 (q, *J*=7.07 Hz, 2 H) 7.40 (s, 1 H) 7.54 (ddd, *J*=7.47, 4.79, 1.04 Hz, 1 H) 7.56 (dt, *J*=8.02, 0.93 Hz, 1 H) 7.99 - 8.04 (m, 1 H) 8.52 (ddd, *J*=4.82, 1.89, 0.85 Hz, 1 H);

ethyl 6-(dimethylamino)methylene-1-(3,3-dimethylaminobutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate;

ethyl 6-(dimethylamino)methylene-2-(3,3-dimethylaminobutyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate;

ethyl 6-[(dimethylamino)methylene]-7-oxo-1-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.88 (2m, 4 H) 3.10 (s, 6 H) 4.33 (q, *J* 7.07 Hz, 2 H) 5.45 (q, *J* 8.90 Hz, 2 H) 7.50 (bs, 1 H);

ethyl 6-[(dimethylamino)methylene]-7-oxo-2-(2,2,2-trifluoroethyl)-4,5,6,7-tetrahydro-2H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,28 (t, *J* 7.07 Hz, 3 H) 2.82 (2m, 4 H) 3.12 (s, 3 H) 4.29 (q, *J* 7.07 Hz, 2 H) 5.57 (q, *J* 9.02 Hz, 2 H) 7.53 (bs, 1 H);

ethyl 6-[(dimethylamino)methylene]-7-oxo-1-phenyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 1-benzyl-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 6-[(dimethylamino)methylene]-1-(1-methylpiperidin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 6-[(dimethylamino)methylene]-7-oxo-1-piperidin-4-yl-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate

ethyl 1-(1-benzylpiperidin-4-yl)-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, *J*=7.07 Hz, 3 H) 1.76 - 2.15 (m, 4 H) 2.79 - 3.01 (m, 4 H) 3.13 (s, 6 H) 3.24 - 3.64 (m, 6 H) 4.29 (q, *J*=7.07 Hz, 2 H) 5.30 (dd, *J*=17.01, 7.26 Hz, 1 H) 7.14 - 7.40 (m, 6 H);

ethyl 1-(1-acetylpiperidin-4-yl)-6-[(dimethylamino)methylene]-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

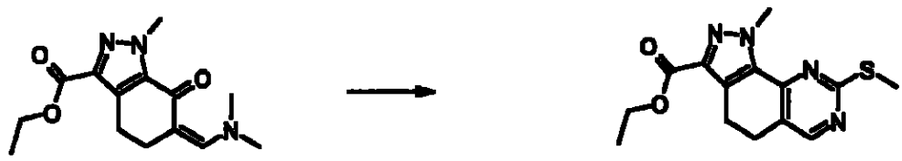
ethyl 6-[(dimethylamino)methylene]-1-(1-formylpiperidin-4-yl)-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 1-(2-dimethylaminoethyl)-6-dimethylaminomethylene-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

ethyl 1-(2-dimethylaminopropyl)-6-dimethylaminomethylene-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

Example 8

Ethyl 1-methyl-8-(methylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B67-X04-M00(C01)-D01]



9 g (69 mmol) of ethyl-6-[(dimethylamino)methylene]-1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 350 mL of anhydrous dimethylformamide and 13.4 g of anhydrous potassium acetate (138 mmol) and 19.18 g (69 mmol) of methylisothiourea sulfate were added. The mixture was maintained at 90°C under stirring for 8 hours. The solvent was then evaporated, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The crude was finally triturated with diethyl ether and collected by filtration to give 15.5 g (74 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.54 (s, 3 H) 2.84-3.00 (m, 4 H) 4.26 (q, *J* 7.07 Hz, 2 H) 4.31 (s, 3 H) 8.53 (m, 1 H).

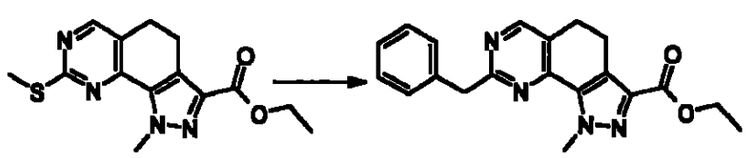
Following the same method, but employing the suitable substituted isothiourea derivative, the following compounds can be prepared:

ethyl 8-(benzylthio)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B05-X04-M00(C01)-D01];

ethyl 1-methyl-8-(phenylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X04-M00(C01)-D01].

Example 9

Ethyl 8-benzyl-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B05-X06-M00(C01)-D01]



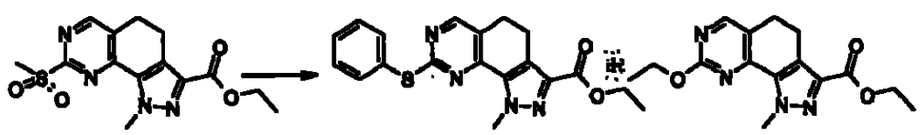
Under a nitrogen atmosphere, a 0.5 M solution of benzylzinc bromide in THF (3.11 mL, 1.556 mmol) was added to a mixture of ethyl 1-methyl-8-(methylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (237 mg, 0.778 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.0078 mmol, 1%). After 20 hours of heating at 60 °C under nitrogen, the mixture was

cooled to room temperature, shaken with aqueous sodium bicarbonate and ethyl acetate and then filtered. The organic phase was then separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic phase was dried over Na_2SO_4, evaporated and the crude was purified on silica gel (eluant dichloromethane/methanol 97/3). 20 mg of the title compound were isolated.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.99 (m, 4 H) 4.23 (s, 2 H) 4.27 (m, 5 H) 7.23 (m, 1 H) 7.32 (m, 2 H) 7.36 (m, 2 H) 8.66 (s, 1 H)

Example 10

ethyl 1-methyl-8-(phenylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X04-M00(C01)-D01]



To a stirred suspension of ethyl 1-methyl-8-(methylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (46 mg, 0.137 mmol) and phenylthiol (16 µl, 17 mg, 0.15 mmol) in ethanol (1 mL), 1*N* sodium hydroxide (150 µl, 0.15 mmol) was added at room temperature under an argon atmosphere. After the mixture was stirred for 3 days, 1*N* hydrochloric acid (150 µl, 0.15 mmol) was added and the solvent removed under vacuo. By chromatography on silica gel (eluant: dichloromethane/methanol 97/3), 13 mg of ethyl 1-methyl-8-(phenylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate and 10 mg of ethyl 8-ethoxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were isolated.

B04-X04-M00(C01)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 2.86 (t, 2 H) 2.93 (t, 2 H) 3.68 (s, 3 H) 4.25 (q, 2 H) 7.48 (m, 3 H) 7.64 (m, 2 H) 8.53 (s, 1 H);

B03-X03-M00(C01)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 1.38 (t, 3 H) 2.91 (t, 2 H) 3.01 (t, 2 H) 4.33 (m, 5 H) 4.41 (q, 2 H).

Example 11

1-methyl-8-(methylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B67-X04-M00(C01)-D03]



13.00 g (0.043 mol) of ethyl 1-methyl-8-(methylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were suspended in a mixture of 200 mL of methanol, 200 mL of dimethylformamide and 200 mL of ammonium hydrate 30 %. The mixture was stirred at 65°C in a closed bottle for about 8 hours. The solvent was then evaporated to dryness, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The crude was purified by chromatography on a silica gel column eluted by a mixture cyclohexane/ethyl acetate, giving 6.16 g (52 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.54 (s, 3 H) 2.75-3.05 (m, 4 H) 4.28 (s, 3 H) 7.47 (bs, 2 H) 8.51 (m, 1 H).

Example 12

1-methyl-8-(methylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B67-X05-M00(C01)-D03]



6.00 g (0.022 mol) of 1-methyl-8-(methylthio)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide were dissolved in 1000 mL of dimethylformamide and 40.18 g of oxone were added. The mixture was stirred 16 hours at room temperature. Water and ethyl acetate were then added and the layers separated. The organic layer was finally dried over Na_2SO_4 and evaporated. The residue was triturated with diethyl ether and 5.40 g (80 % yield) of the title compound were collected by filtration.

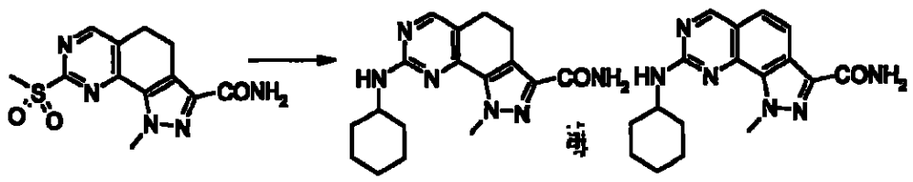
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (m, 4 H) 3.43 (s, 3 H) 4.29 (s, 3 H) 7.45 (bs, 2 H) 8.91 (m, 1 H).

By working according to this methodology the following compound was prepared:

ethyl 1-methyl-8-(methylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B67-X05-M00(C01)-D01]

Example 13

8-(cyclohexylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B27-X00-M00(C01)-D03] and 8-(cyclohexylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B27-X00-M01(C01)-D03]



1.5 g of 1-methyl-8-(methylsulfonyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide were dissolved in 100 mL of dry dimethylsulfoxide and 1.15 mL of cyclohexylamine were added. After 16 hours at 80°C under nitrogen the solvent was evaporated at reduced pressure. The residue was then redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. By chromatography on a silica gel column (eluant dichloromethane/acetone 9/1) 300 mg of 8-(cyclohexylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide and 200 mg of 8-(cyclohexylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide and were obtained (30% yield overall).

B27-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (m, 10 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.69 (m, 1 H) 4.31 (m, 3 H) 6.94 (d, *J* 6.58 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H);

B27-X00-M01(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (m, 10 H) 3.88 (m, 1 H) 4.66 (s, 3 H) 7.40 (s, 1 H) 7.47 (d, *J* 8.66 Hz, 1 H) 7.59 (s, 1 H) 7.74 (s, 1 H) 7.87 (d, *J* 8.66 Hz, 1 H) 9.13 (s, 1 H)

By working according to this methodology, and by taking into account that when the amine is available as a salt, stoichiometric amounts of potassium carbonate were employed, the following compounds were prepared as coded in Table VI:

Table VI

B76-X06-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 6 H) 2.75 (m, 2 H) 2.96 (m, 2 H) 3.76 (m, 4 H) 4.29 (s, 3 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.29 (s, 1 H)

B23-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSOd$_6$) δ ppm 2.21 (s, 6 H) 2.46 (m, , 2 H) 2.74 (m, 2 H) 2.95 (m, , 2 H) 3.41 (m, 2 H) 4.32 (s, 3 H) 6.90 (t, *J* 5.73 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B24-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.69 (m, 4 H); 2.49 (m, 4 H); 2.95 and 2.61 (2m, 4 H); 3.40 (m, 2 H); 4.32 (s, 3 H); 6.95 (bs, NH); 7.2-7.4 (2s, 2 H); 8.21 (s, 1 H).
B25-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.51 (m, 6 H) 2.52 (m, 6 H) 2.70 (m, 2 H,) 2.95 (m, 2 H,) 3.42 (m, 2 H) 4.32 (s, 3 H) 7.2-7.4 (2s, 2 H) 8.21 (s, 1 H).
B26-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.37-2.54 (m, 6 H) 2.74 (m, 2 H,) 2.95 (m, 2 H.) 3.45 (m, 2 H) 3.59 (m, 4 H) 4.32 (s, 3 H) 6.93 (bs, NH) 8.22 (s, 1 H).
B28-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.18 (m, 11 H) 2.72 (m, 2 H) 2.94 (m, 2 H,) 3.16 (m, 2 H) 4.31 (s, 3 H) 7.14-7.49 (3bs, 3 H) 8.19 (s, 1 H).
B29-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 1.00 (m, 3 H) 2.60-3.20 (m, 10H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.88 (m, 1 H) 4.31 (s, 3 H) 6.88 (bs, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.22 (s, 1 H).
B30-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.98 (m, 2 H) 3.07 (m, 2 H) 4.34 (s, 3 H) 6.60 (m, 2 H) 7.44 (m, 2 H) 7.32 (s, 1 H) 8.71 (s, 1 H).
B31-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.62 (d, *J* 6.10 Hz, 2 H) 7.23 (m, 2 H) 7.34 (m, 1 H) 7.41 (s, 1 H) 7.73 (m, 2 H) 8.24 (s, 1 H) 8.50 (m, 1 H).
B32-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.86 (m, 4 H) 4.17 (s, 3 H) 4.56 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.34 (dd, *J* 7.87, 4.69 Hz, 1 H) 7.42 (s, 1 H) 7.74 (m, 1 H) 7.74 (dt, *J* 7.68, 1.83 Hz, 1 H) 8.24 (s, 1 H) 8.44 (dd, *J* 4.76, 1.46 Hz, 1 H) 8.57 (d, *J* 1.83 Hz, 1 H)
B33-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 4.55 (d, J 6.22 Hz, 2 H) 7.22 (s, 1 H) 7.32 (m, 2 H) 7.41 (s, 1 H) 7.78 (bs, 1 H) 8.24 (s, 1 H) 8.49 (m, 2 H).
B34-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.73 (m, 2 H) 2.94 (m, 2 H) 4.62 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.54-7.76 (2m, 4 H) 7.82 (bs. 1 H) 8.24 (s, 1 H).
B35-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.23 (s, 3 H) 4.44 (d, *J* 6.22 Hz, 2 H) 5.97 (s, 2 H) 6.83 (m, 2 H) 6.91 (s, 1 H) 7.23 (s, 1 H);7.42 (s, 1 H) 7.63 (bs, 1 H) 8.23 (s, 1 H).

B37-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.73 (m, 2 H) 1.93 (m, 2 H) 2.22 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.34 (m, 4 H) 4.32 (s, 3 H) 7.09 (bs, 1 H) 7.22 (s, 1 H) 7.43 (s, 1 H) 8.22 (s, 1 H).
B38-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.81 (t, *J* 7.38 Hz, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.54 (m, 2 H) 4.32 (s, 3 H) 6.86 (s, 1 H) 7.16 (t, *J* 5.55 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.61 (s, 1 H) 8.22 (s, 1 H) 12.00 (s, 1 H)
B39-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (m, 2 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.33 (m, 4 H) 4.25 (s, 3 H) 6.99 (s, 1 H) 7.27 (m, 3 H) 7.24 (s, 3 H) 7.43 (s, 1 H) 7.80 (s, 1 H) 8.22 (s, 1 H).
B40-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.44 (m, *J* 4.39 Hz, 4 H) 2.83 (m, 4 H) 3.10 (m, 4 H) 4.20 (s, 3 H) 4.47 (d, *J* 6.22 Hz, 2 H) 6.78 (m, 2 H) 6.94 (m, 1 H) 7.13 (m, 1 H) 7.22 (s, 1 H) 7.41 (s, 1 H) 7.63 (s, 1 H) 8.22 (s, 1 H)
B41-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.52 (m, 4 H) 2.83 (m, 4 H) 3.11 (s, 4 H) 4.22 (s, 3 H) 4.43 (d, *J* 6.22 Hz, 2 H) 6.88 (d, *J* 8.78 Hz, 2 H) 7.20 (d, *J* 8.66 Hz, 2 H) 7.23 (s, 1 H) 7.41 (t, 1 H) 7.57 (t, *J* 6.10 Hz, 1 H) 8.21 (s, 1 H)
B42-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (m, 2 H) 2.95 (m, 2 H) 4.27 (s, 3 H) 4.71 (d, *J* 6.22 Hz, 2 H) 6.96 (m, 1 H) 7.32 (m, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.73 (s, 1 H) 8.26 (s, 1 H).
B44-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 4 H) 4.27 (s, 3 H) 4.52 (d, *J* 5.97 Hz, 2 H) 6.24 (d, *J* 2.68 Hz, 1 H) 6.38 (dd, *J* 3.11, 1.89 Hz, 1 H) 7.23 (m, *J* 0.49 Hz, 1 H) 7.43 (s, 1 H) 7.56 (m, *J* 0.98 Hz, 2 H) 8.24 (s, 1 H)
B45-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.5-1.9 (3m, 4 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.33 (m, 2 H) 3.6-3.8 (2m, 2 H) 4.05 (m, 1 H) 4.31 (s, 3 H) 7.10 (bs, 1 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H).
B46-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, *J*=7.62 Hz, 2 H) 2.93 (t, *J*=7.68 Hz, 2 H) 3.73 (s, 3 H) 4.19 (s, 3 H) 4.51 (d, *J*=6.34 Hz, 2 H) 6.74 - 6.82 (m, 1 H) 6.87 - 6.96 (m, 2 H) 7.16 - 7.30 (m, 2 H) 7.41 (s, 1 H) 7.68 (t, *J*=6.65 Hz, 1 H) 8.23 (s, 1 H)
B47-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (none, 2 H) 2.81 (m, 4 H) 3.10 (none, 1 H) 4.34 (s, 3 H) 7.00 (s, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.18 (s, 1 H)
B48-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (s, 6 H) 2.14 (s, 3 H) 2.22 (m, *J* 2.07 Hz, 6 H) 4.70 (s, 3 H) 7.19 (s, 1 H) 7.41 (s, 1 H) 7.48 (d, *J* 8.66 Hz, 1 H)

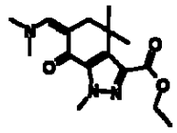
	7.76 (s, 1 H) 7.91 (d, *J* 8.66 Hz, 1 H) 9.13 (s, 1 H)
B49-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 (s, 3 H) 1.04 (d, *J* 7.07 Hz, 3 H) 1.19 (s, 3 H) 1.4-2.4 (5m, 8H) 2.70-3.00 (2t, 4 H) 3.34 (bs, 2 H) 4.35 (s, 3 H) 7.23-7.42 (3bs, 3 H) 8.20 (s, 1 H)
B50-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 2 H) 1.91 (d, *J* 11.71 Hz, 2 H) 2.06 (m, 2 H) 2.73 (m, *J* 7.93, 7.44 Hz, 2 H) 2.83 (d, *J* 11.34 Hz, 2 H) 2.94 (t, *J* 7.62 Hz, 2 H) 3.48 (s, 2 H) 3.70 (m, 1 H) 4.30 (s, 3 H) 7.01 (d, *J* 4.51 Hz, 1 H) 7.23 (s, 1 H) 7.30 (m, 5 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B51-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, *J*=7.62 Hz, 2 H) 2.93 (t, *J*=7.68 Hz, 2 H) 4.10 (s, 3 H) 4.60 (d, *J*=6.10 Hz, 2 H) 7.22 (s, 1 H) 7.27 (s, 2 H) 7.41 (s, 1 H) 7.51 (d, *J*=8.54 Hz, 2 H) 7.77 (d, *J*=8.41 Hz, 2 H) 7.78 - 7.83 (m, 1 H) 8.23 (s, 1 H)
B52-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 3.18 (s, 3 H) 4.63 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.59 (m, 2 H) 7.86 (m, 3 H) 8.24 (s, 1 H).
B53-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.11 (m, 4 H) 4.37 (s, 3 H) 4.43 (s, 3 H) 7.37 (m, 4 H) 7.57 (s, 1 H) 7.74 (m, 2 H) 8.20 (m, 2 H) 8.92 (s, 1 H).
B54-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 and2.93 (2t, 4 H, J 8.04 Hz) 4.18 (s, 3 H) 4.49 (d, 2 H, 6.34 Hz) 7.13 (m, 1 H) 7.36 (m, 1 H) 7.42 and 7.23 (2s, 2 H) 7.58 (m, 1 H) 7.73 (bs, 2 H) 8.23 (s, 1 H).
B55-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.24 (m, 2 H) 0.44 (m, 2 H) 1.13 (m, 1 H) 2.74 (m, 2 H) 2.95 (t, *J* 7.68 Hz, 2 H) 3.20 (m, 2 H) 4.32 (s, 3 H) 7.17 (t, *J* 5.79 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B56-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.80 Hz, 2 H) 3.51 - 3.75 (m, 2 H) 4.04 (dd, *J*=11.52, 6.77 Hz, 1 H) 4.27 (s, 3 H) 4.34 (dd, *J*=11.58, 2.19 Hz, 1 H) 4.38 - 4.48 (m, 1 H) 6.74 - 6.94 (m, 4 H) 7.24 (s, 1 H) 7.36 (t, *J*=5.97 Hz, 1 H) 7.44 (s, 1 H) 8.25 (s, 1 H)
B57-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.14 (bs, 3 H) 4.62 (d, , *J* 6.22 Hz2 H) 7.23 (s, 1 H) 7.42 (s, 1 H) 7.51 (m, 2 H) 7.60 (m, 1 H) 7.83 (bs, 1 H) 9.26 (s, 1 H).
B58-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.95 (m, 2 H) 3.05 (m, 2 H) 3.69 (m, 2 H) 4.33 (s, 3 H) 7.24 (3m, 3 H) 7.32 (m, 1 H), 7.43 /m, 1 H) 8.22 (s, 1 H) 8.51 (m, 1 H).
B59-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 and 2.93 (2t, 4 H, J 7.56) 4.18 (s, 3 H) 6.27 (2s, 2 H) 7.22 (m,

	1 H) 7.31 (2s, 2 H) 7.37-7.43 (2m, 2 H) 7.55 (s, 1 H) 7.74 (bs, 1 H) 8.24 (s, 1 H).
B30-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.72 (s, 3 H) 6.67 (m, 1 H) 7.56 (m, 1 H) 7.44 (s, 1 H) 7.63 (s, 1 H) 8.33 (m, 1 H) 8.35 (m, 1 H) 9.73).
B45-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50-2.00 (2m, 4 H) 3.34 (m, 2 H) 3.67-3.69 (2m, 2 H) 4.18 (m, 1 H) 4.67 (s, 3 H) 7.42 (m, 1 H) 7.74 (m, 2 H) 7.88 (m, 1 H) 7.88 (m, 1 H) 9.15 (s, 1 H).
B28-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90-2.00 (6m, 11 H) 3.34 (m, 2 H) 4.67 (s, 3 H) 7.41 (bs, 1 H) 7.48 (m, 2 H) 7.86 (m, 1 H) 9.12 (s, 1 H).
B29-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.04 (m, 1 H) 4.66 (s, 3 H) 7.42 (bs, 1 H) 7.50 (m, 1 H) 7.70 (s, 1 H) 7.88 (m, 1 H) 9.15 (s, 1 H).
B50-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.65 (s, 3 H) 7.00-8.00 (m, 9H) 9.14 (s, 1 H).
B55-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 0.31 (m, 2 H) 0.49 (m, 2 H) 1.25 (m, 1 H) 3.33 (m, 2 H) 4.68 (s, 3 H) 7.41 (s, 1 H) 7.49 (m, 2 H) 7.73 (s, 1 H) 7.75 (s, 1 H) 9.14 (s, 1 H).
B01-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (m, 4 H) 3.40 (m, 4 H) 4.31 (s, 3 H) 4.66 (s, 1 H) 6.96 (t, *J* 5.67 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B02-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.50 (m, 2 H) 4.32 (s, 3 H) 4.45 (m, 1 H) 7.05 (bs, 1 H) 7.23 (s, 1 H) 7.42 (s, 1 H) 8.20 (s, 1 H).
B05-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 4.17 (bs, 3 H) 4.55 (d, *J* 6.22 Hz, 2 H) 7.15-7.40 (m, 7H) 7.70 (bs, 1 H) 8.23 (s, 1 H).
B69-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 2.74 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.68 Hz, 2 H) 3.44 (s, 3 H) 4.32 (s, 3 H) 4.46 (d, *J*=5.73 Hz, 2 H) 5.66 (dd, *J*=3.41, 0.73 Hz, 1 H) 5.84 (d, *J*=3.29 Hz, 1 H) 7.24 (s, 1 H) 7.28 (t, *J*=4.94 Hz, 1 H) 7.43 (s, 1 H) 8.24 (s, 1 H)
B70-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 and 2.95 (2t, 4 H, J 7.32 Hz) 4.24 (s, 3 H) 4.57 (d, 2 H, J 6.22 Hz) 6.13 (s, 1 H) 7.23 and 7.43 (2s, 2 H) 7.64 (bs, 1 H) 8.25 (s, 1 H)
B71-X00-M00(C01)-D03	
B72-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, *J*=7.62 Hz, 2 H) 2.94 (t, *J*=7.62 Hz, 2 H) 4.20 (s, 3 H) 4.58 (d, *J*=6.22 Hz, 2 H) 6.53 (dd, *J*=2.50, 1.77

	Hz, 1 H) 7.22 (s, 1 H) 7.41 (s, 1 H) 7.46 (d, *J*=8.66 Hz, 2 H) 7.72 (dd, *J*=1.71, 0.49 Hz, 1 H) 7.74 - 7.77 (m, 1 H) 7.77 (d, *J*=8.66 Hz, 2 H) 8.24 (s, 1 H) 8.43 (dd, *J*=2.50, 0.55 Hz, 1 H)
B74-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.96 (m, 2 H) 3.16 (s, 6 H) 4.43 (s, 3 H) 7.23 (bs, 1 H) 7.43 (bs, 1 H) 8.28 (s, 1 H).

Example 14

Ethyl 6-[(dimethylamino)methylene]-1,4,4-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



Step 1. 3-methoxy-5,5-dimethyl-cyclohex-2-enone



A solution of 5,5-dimethyl-cyclohexane-1,3-dione (80.0 g, 0.57 mol) in anhydrous methanol (600 mL) was treated with a 1 M solution of titanium chloride ($TiCl_4$) in dichloromethane (17.2 mL). After stirring 1 hour at room temperature, the mixture was slowly poured into cold 5% $NaHCO_3$ solution and extracted with diethyl ether (450 mL x 6). The organic layers were collected, washed with brine, dried on Na_2SO_4 and evaporated to dryness affording the title compound (81.5 g, 92% yield) as a pale yellow oil.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.05 (s, 6 H) 2.19 (s, 2 H) 2.26 (s, 2 H) 3.68 (s, 3 H) 5.35 (s, 1 H).

Step 2. 5,5-dimethyl-cyclohex-2-enone



A solution of 3-methoxy-5,5-dimethyl-cyclohex-2-enone (80 g, 0.52 mol) in anhydrous tetrahydrofuran (270 mL) was treated dropwise with a 1 M solution of $LiAlH_4$ in tetrahydrofuran (182 mL), under argon atmosphere and keeping the temperature of the reaction between 0°C and 5°C. The temperature was allowed to rise to 25°C and the

mixture was stirred for 4 hours. The resulting slurry was cooled with an ice bath, quenched with ethyl acetate (30 mL) and poured with caution into a cooled 2 M H_2SO_4 solution. The aqueous solution was then extracted with diethyl ether (300 mL x 3), dried on Na_2SO_4 and evaporated under reduced pressure to remove most of the solvent. The crude material contained the title compound as a low boiling point oil that was used in the next step without further purification.

^{1}H NMR (300 MHz, $CHCL_3$-d) δ ppm 1.04 (s, 6 H) 2.23 (dd, *J* 4.10, 2.05 Hz, 2 H) 2.27 (s, 2 H) 6.02 (dt, *J* 9.96, 2.05 Hz, 1 H) 6.85 (dt, *J* 9.96, 4.10 Hz, 1 H).

Step 3. 4,4-dimethyl-7-oxa-bicyclo[4.1.0]heptan-2-one



5,5-dimethyl-cyclohex-2-enone from the previous step (0.52 mol theoretically) was dissolved in methanol (500 mL), cooled to 0°C and treated wit 30% hydrogen peroxide (265 mL, 2.6 mol). The resulting solution was treated dropwise with a 2% NaOH solution (142 mL, 0.067 mol) keeping the reaction temperature around 0°C. The mixture was allowed to stay at 4°C for twenty hours and was then diluted with water (900 mL) and extracted with ethyl ether (450 mL x 4).

The extracts were collected, washed with 5% $Na_2S_2O_5$ solution, with brine, dried on Na_2SO_4 and concentrated under reduced pressure. The residue was purified by distillation under vacuum to obtain the title compound (56.8 g, 78.3% yield) as a colourless oil.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 0.91 (s, 3 H) 1.01 (s, 3 H) 1.82 (m, 2 H) 2.03 (d, *J* 15.53 Hz, 1 H) 2.64 (d, *J* 13.77 Hz, 1 H) 3.20 (dt, *J* 3.74, 0.92 Hz, 1 H) 3.49 (t, *J* 4.10 Hz, 1 H).

Step 4. 2-methoxy-5,5-dimethyl-cyclohex-2-enone

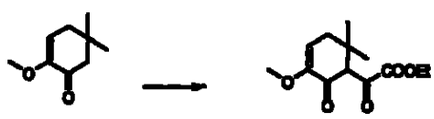


A solution of 4,4-dimethyl-7-oxa-bicyclo[4.1.0]heptan-2-one (44.0 g, 0.31 mol) in methanol (150 mL) was added to a solution of 85% potassium hydroxide (20.7 g, 0.31 mol) in methanol (450 mL) at room temperature. The mixture was kept at this temperature for 20 hours and was then heated to reflux for 30 minutes. After cooling,

the solution was diluted with water (1.2 L) and extracted wit ethyl ether (350 mL x 5). The organic extracts were collected, washed with brine, dried on Na_2SO_4 and evaporated under vacuum to remove most of the solvent. The crude material was purified by distillation to obtain pure the title compound (32.8 g, 68% yield) as an oil.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.04 (s, 6 H) 2.30 (d, *J* 4.69 Hz, 2 H) 2.35 (s, 2 H) 3.59 (t, 3 H) 5.67 (t, *J* 4.54 Hz, 1 H).

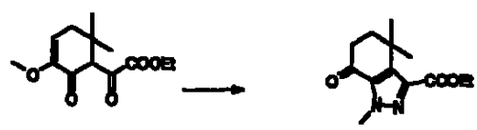
Step 5. Ethyl (3-methoxy-6,6-dimethyl-2-oxocyclohex-3-en-1-yl)(oxo)acetate



60% sodium hydride in mineral oil (2.41 g, 60.3 mmol) was suspended in anhydrous tetrahydrofuran (60 mL) under argon atmosphere and treated with a solution of 2-methoxy-5,5-dimethyl-cyclohex-2-enone (6.20 g, 40.2 mmol) in anhydrous tetrahydrofuran (50 mL). After 15 minutes, a solution of diethyl oxalate (8.17 mL, 60.3 mmol) in anhydrous tetrahydrofuran (50 mL) was added and the mixture was refluxed for 1 hour. The slurry was diluted with water (800 mL), acidified with 1 N HCl (50 mL) and extracted with ethyl acetate (500 mL x 2). The organic layers were collected, washed with brine, dried on Na_2SO_4 and evaporated to dryness to obtain the crude title compound (10.60 g) as an orange oil, which was used without further purification.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.41 (t, 3 H) 2.77 (s, 2 H) 3.13 (s, 6 H) 4.23 (s, 3 H) 4.40 (q, *J* 7.13 Hz, 2 H) 7.58 (s, 1 H).

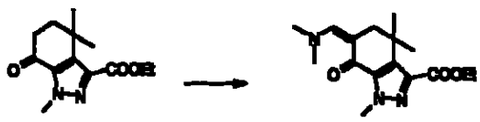
Step 6. Ethyl 1,4,4-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



A solution of ethyl (3-methoxy-6,6-dimethyl-2-oxocyclohex-3-en-1-yl)(oxo)acetate from the previous step (40.2 mmol theoretically) in acetic acid (65 mL) was treated dropwise with a solution of methyl hydrazine (2.14 mL, 40.2 mmol) in acetic acid (20 mL) and allowed to stand at room temperature overnight. The mixture was then diluted with water (800 mL) and extracted with ethyl acetate (500 mL x 2). The organic extracts were washed with brine, dried on Na_2SO_4 and evaporated to dryness. The crude material was chromatographed on silica gel eluted with dichloromethane/ethyl acetate 100:5 to obtain the pure title compond (4.8 g, 47.7% yield).

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.42 (t, *J* 7.18 Hz, 3 H) 1.49 (s, 3 H) 1.98 (t, *J* 6.45 Hz, 2 H) 2.61 (t, *J* 6.45 Hz, 2 H) 4.19 (s, 3 H) 4.43 (q, *J* 7.03 Hz, 2 H)

Step 7. Ethyl 6-[(dimethylamino)methylene]-1,4,4-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

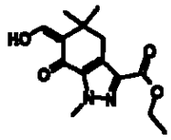


A solution of ethyl 1,4,4-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (4.8 g, 19.18 mmol) in anhydrous dimethylformamide (30 mL) was treated with dimethylformamide di-tert-butylacetal (9.19 mL, 38.35 mmol) at 65°C for 2 hours. The mixture was evaporated to dryness and the crude material was crystallized from hexane to give the title compound (5.1 g, 87% yield).

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.21 (m, 9H) 2.76 (s, 2 H) 3.15 (s, 6 H) 4.22 (s, 3 H) 4.41 (q, 2 H).

Example 15

Ethyl 6-(hydroxymethylene)-1,5,5-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



Step 1. 5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one



A solution of 4,4-dimethyl-cyclohex-2-enone (32.0 g, 0.26 mol) and 30% hydrogen peroxide (132 mL, 1.29 mol) in methanol (250 mL) was treated dropwise with a 2% sodium hydroxide solution (70 mL, 0.035 mol) keeping the reaction temperature around 0°C. The mixture was allowed to stay at 4°C for 20 hours and was then diluted with water (400 mL) and extracted with diethyl ether (250 mL x 4).

The extracts were collected, washed with 5% $Na_2S_2O_5$ solution, with brine, dried on Na_2SO_4 and concentrated under reduced pressure. The residue was purified by distillation under vacuum to obtain the title compound (27.6 g, 76.4% yield) as an oil.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.05 (s, 3 H) 1.21 (s, 3 H) 1.20-2.50 (m, 5 H) 3.20 (m, 1 H).

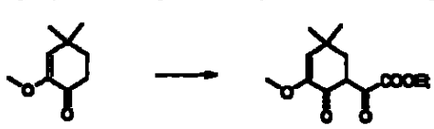
Step 2. 2-methoxy-4,4-dimethylcyclohex-2-en-1-one



A solution of 5,5-dimethyl-7-oxabicyclo[4.1.0]heptan-2-one (19.4 g, 138.4 mmol) in methanol (95 mL) was added to a solution of 85% potassium hydroxide (9.1 g, 138.4 mmol) in methanol (285 mL) at room temperature. The mixture was kept at this temperature for 20 hours and was then heated to reflux for 30 minutes. After cooling, the solution was diluted with water (750 mL) and extracted with diethyl ether (350 mL x 4). The organic extracts were collected, washed with brine, dried on Na_2SO_4 and evaporated to dryness. The crude material was taken up with hexane (380 mL), maintained under vigorous stirring for 30 minutes and filtered to remove the solid material. The filtrate was evaporated under vacuum to obtain the pure title compound (9.8 g, 45.9% yield) as a pale yellow oil.

^{1}H NMR ($CDCl_3$ 400 MHz) δ ppm 1.23 (s, 6 H) 1.87 (t, 2 H) 2.61 (t, 2 H) 3.60 (s, 3 H) 5.57 (s, 1 H)

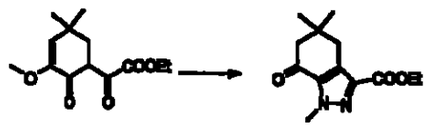
Step 3. Ethyl (3-methoxy-5,5-dimethyl-2-oxocyclohex-3-en-1-yl)(oxo)acetate



A solution of 2-methoxy-4,4-dimethyl-cyclohex-2-enone (12.5 g, 81.1 mmol) and diethyl oxalate (12.1 mL, 89.2 mmol) in ethyl ether was treated with a 1 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran under argon atmosphere. The reaction was stirred at room temperature for 2 hours, poured into a 10% NaH_2PO_4 solution (500 mL) and extracted with diethyl ether (300 mL x 2). The organic extracts were washed with brine, dried on Na_2SO_4 and evaporated to dryness. The crude material was taken up with hexane, stirred and filtered to give the title compound (16.8 g, 81.5% yield) as a yellow crystalline solid.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.15 (s, 6 H) 1.38 (t, 3 H) 2.77 (s, 2 H) 3.63 (s, 3 H) 4.35 (q, 2 H) 5.62 (s, 1 H).

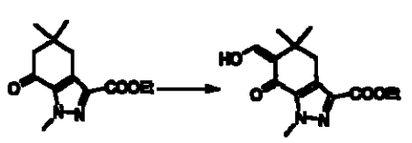
Step 4. Ethyl 1,5,5-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



A solution of ethyl (3-methoxy-5,5-dimethyl-2-oxocyclohex-3-en-1-yl)(oxo)acetate (15.50 g, 0.061 mol) in acetic acid (100 mL) was treated dropwise with a solution of methyl hydrazine (3.49 mL, 0.066 mol) dissolved in acetic acid (50 mL). After 24 hours at room temperature, the reaction mixture was diluted with water (2 L) under vigorous stirring. The resulting precipitate was filtered and washed with water to obtain the title compound (10.30 g, 67.6% yield) as a yellow solid.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.20 (s, 6 H) 1.42 (t, 3 H) 2.43 (s, 2 H) 2.93 (s, 2 H) 4.21 (s, 3 H) 4.41 (q, 2 H).

Step 5. Ethyl 6-(hydroxymethylene)-1,5,5-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



A solution of ethyl 1,5,5-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (1.00 g, 4 mmol) in anhydrous ethyl formate (10 mL) was treated with sodium ethoxide (0.54 g, 8 mmol) and refluxed for 3 hours. The mixture was cooled to room temperature and poured into cold water (40 mL). The aqueous layer was washed with diethyl ether (40 mL) to remove unreacted starting material, acidified with a 20% NaH_2PO_4 solution and extracted with ethyl acetate (50 mL x 2). The organic extracts were collected, dried on Na_2SO_4 and evaporated to dryness to obtain the title compound (0.88 g, 78.8% yield) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 6 H) 1.32 (t, 3 H) 2.87 (s, 2 H) 4.19 (s, 3 H) 4.30 (q, 2 H) 7.74 (s, 1 H) 14.00 (br, 1 H)

Example 16

Ethyl 8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

[B00-X00-M00(C01)-D01]



16.00 g (0.06 mol) of ethyl-6-[(dimethylamino)methylene]-1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 600 mL of ethanol and 3.90 g of sodium ethylate, and 5.44 g of guanidine hydrochloride were added consecutively. The solution was stirred at reflux for 12 hours. The solvent was then evaporated, the residue redissolved with dichloromethane and washed with water. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated with diethyl ether and the product collected by filtration (85 % yield as a white solid).
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.28 (t, *J* 7.07 Hz, 3 H) 2.68-2.93 (m, 4 H) 4.25 (q, *J* 7.07 Hz, 2 H) 4.30 (s, 3 H) 6.54 (bs, 2 H) 8.15 (m, 1 H).

According to this same methodology, but employing a suitable substituted guanidine derivative, the following compounds were prepared, as reported in table VII:

Table VII

B04-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.82 (m, 2 H) 2.95 (m, 2 H) 4.27 (q, *J* 7.07 Hz, 2 H) 4.32 (s, 3 H) 6.93 (m, 2 H) 7.37 (m, 2 H) 7.77 (m, 2 H) 8.39 (s, 1 H) 9.49 (s, 1 H).
B06-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.84 (m, 2 H) 2.96 (m, 2 H) 4.27 (q, *J* 7.07 Hz, 2 H) 6.97 (m, 1 H) 7.30 (m, 1 H) 7.54 (m, 1 H) 7.97 (m, 1 H) 8.42 (s, 1 H) 9.74 (s, 1 H).
B07-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.85 (m, 2 H) 2.97 (m, 2 H) 4.28 (q, *J* 7.07 Hz, 2 H) 4.33 (s, 3 H) 7.28 (m, 1 H) 7.51 (m, 1 H) 7.89 (m, 2 H) 8.18 (bs, 1 H) 8.47 (s, 1 H) 9.88 (s, 1 H).
B08-X00-M00(C01)-D01	
B09-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.21 (s, 3 H,) 2.45 (m, 2 H) 2.81 (m, 2 H) 2.95 (m, 2 H) 3.69 (m, 4 H) 4.26 (q, *J* 7.07 Hz, 2 H) 4.33 (s, 3 H) 6.65 (m, 1 H) 7.10 (m, 1 H) 7.19 (m, 1 H) 7.21 (m, 1 H) 8.38 (s, 1 H) 9.31 (bs, 1 H).
B10-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.19 Hz, 3 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.84 (t, *J*=7.74 Hz, 2 H) 2.99 (t, *J*=7.74 Hz, 2 H) 3.10 (m, 4 H) 4.32 (q, *J*=7.19 Hz, 2 H) 4.36 (s, 3 H) 6.93 (d, *J*=9.34 Hz, 2 H) 7.53 (d, *J*=9.34 Hz, 2 H) 8.37 (s, 1 H) 9.29 (s, 1 H)
B04-X00-M00(C02)-D01	
B04-X00-M00(C04)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.82 (m, 2 H) 2.96 (m, 2 H) 3.79 (m, 2 H) 4.28 (q, *J* 7.07 Hz, 2 H) 4.78 (t, *J* 5.25 Hz, OH) 4.88

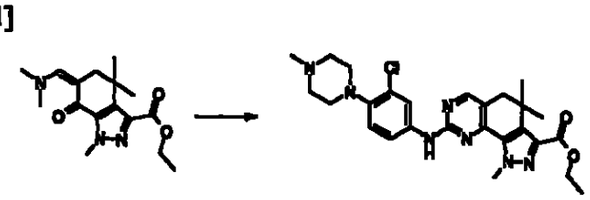
	(t, *J* 5.73 Hz, 2 H) 6.95 (m, 1 H) 7.29 (m, 2 H) 7.65 (m, 2 H) 8.39 (s, 1 H) 9.44 (bs, 1 H).
B04-X00-M00(C06)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H, *J*=7.07 Hz) 1.33 (t, 3 H, *J*=7.07 Hz) 2.90 (m, 2 H) 3.03 (m, 2 H) 4.07 (q, 2 H, *J*=7.07 Hz) 4.31 (q, 2 H, *J*=7.07 Hz) 5.73 (s, 2 H) 7.01 (m, 1 H) 7.31 (m, 2 H) 7.57 (m, 2 H) 8.44 (s, 1 H) 9.49 (bs, 1 H).
B04-X00-M00(C08)-D01	
B04-X00-M00(C09)-D01	
B04-X00-M00(C10)-D01	
B04-X00-M00(C05)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.87 (m, 2 H) 3.02 (m, 2 H) 4.36 (q, *J* 7.07 Hz, 2 H) 5.53 (q, *J* 8.90 H, 2 H) 6.90 (m, 1 H) 7.24 (m, 2 H) 7.79 (m, 2 H) 8.42 (s, 1 H) 9.74 (bs, 1 H).
B04-X00-M04(C05)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.87 (m, 2 H) 2.98 (m, 2 H) 4.29 (q, *J* 7.07 Hz, 2 H) 5.85 (q, *J* 8.90 Hz, 2 H) 6.80-7.60 (3m, 5 H) 8.43 (s, 1 H) 9.58 (bs, 1 H).
B04-X00-M00(C11)-D01	
B36-X00-M00(C01)-D01	
B12-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.93 (m, 8 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.36 (s, 3 H) 7.54 (d, *J* 8.90 Hz, 1 H) 7.93 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.07 (d, *J* 2.56 Hz, 1 H) 8.46 (s, 1 H) 9.78 (s, 1 H)
B13-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.28 (s, 3 H) 2.53 (m, 4 H) 2.94 (m, 8 H) 4.31 (q, *J* 7.15 Hz, 2 H) 4.38 (s, 3 H) 7.14 (d, *J* 8.90 Hz, 1 H) 7.53 (dd, *J* 8.72, 2.50 Hz, 1 H) 7.96 (d, *J* 2.44 Hz, 1 H) 8.44 (s, 1 H) 9.60 (s, 1 H)
B00-X00-M00(C00)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.2 Hz, 3 H) 2.78 (m, 2 H) 2.96 (m, 2 H) 4.31 (q, *J*=7.2 Hz, 2 H) 6.64 (m, 2 H) 8.19 (bs, 1 H)
B00-X00-M00(C03)-D01	
B00-X00-M04(C03)-D01	
B00-X00-M00(C04)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.79 - 3.88 (m, 2 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.80 (t, *J*=5.79 Hz, 1 H) 4.84 (t, *J*=5.97 Hz, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B00-X00-M00(C05)-D01	
B00-X00-M00(C08)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (t, *J*=7.07 Hz, 3 H) 2.83 (t, *J*=7.56 Hz, 2 H) 3.02 (t, *J*=7.38 Hz, 2 H) 4.36 (q, *J*=7.07 Hz, 2 H) 6.14 (s, 2 H) 7.44 (s, 2 H) 7.83 (d, *J*=8.78 Hz, 2 H) 7.92 - 7.99 (m, 2 H) 8.25 (s, 1 H)
B00-X00-M00(C09)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t,

	J=7.13 Hz, 3 H) 2.80 (t, J=7.50 Hz, 2 H) 3.00 (t, J=7.38 Hz, 2 H) 3.85 (s, 3 H) 4.34 (q, J=7.11 Hz, 2 H) 6.10 (s, 2 H) 7.03 (d, J=9.02 Hz, 2 H) 7.50 (d, J=9.02 Hz, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J=7.07 Hz, 3 H) 2.83 (t, J=7.56 Hz, 2 H) 3.01 (t, J=7.68 Hz, 2 H) 4.36 (q, J=7.15 Hz, 2 H) 6.24 (s, 2 H) 7.83 (d, J=8.78 Hz, 2 H) 7.97 (d, J=8.78 Hz, 2 H) 8.23 (s, 1 H)
B00-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J=7.07 Hz, 3 H) 2.83 (t, J=7.50 Hz, 2 H) 3.01 (t, J=7.56 Hz, 2 H) 4.35 (q, J=7.07 Hz, 2 H) 6.02 (s, 2 H) 7.57 (ddd, J=7.53, 4.85, 1.04 Hz, 1 H) 7.68 (dt, J=7.99, 0.95 Hz, 1 H) 8.05 (td, J=7.74, 1.95 Hz, 1 H) 8.21 (s, 1 H) 8.53 (ddd, J=4.88, 1.83, 0.85 Hz, 1 H)
B00-X00-M00(C16)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, 3 H, J = 7.07 Hz) 2.82 and 3.01 (2t, 4 H, J = 7.68 Hz) 4.34 (q, 2 H, J = 7.68 Hz) 6.06 (s, 2 H) 7.46-7.60 (2m, 5 H) 8.22 (s, 1 H)
B00-X00-M00(C17)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J = 7.20 Hz) 2.76 and 2.96 (2t, 4 H, J = 7.31 Hz) 4.29 (q, 2 H, J = 7.20 Hz) 6.09 (s, 2 H) 6.64 (s, 2 H) 7.34 (m, 5 H) 8.19 (s, 1 H)
B00-X00-M00(C20)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.19 Hz) 2.09 (m, 4 H) 3.85 (m, 4 H) 4.31 (q, 2 H, J 7.19 Hz) 5.88 (m, 1 H) 6.67 (bs, 2 H) 8.08 (s, 1 H) 8.21 (s, 1 H).
B00-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 1.93 - 2.16 (m, 4 H) 2.24 - 2.43 (m, 5 H) 2.74 (t, J=7.62 Hz, 2 H) 2.88 - 3.02 (m, 4 H) 4.31 (q, J=7.07 Hz, 2 H) 5.48 - 5.69 (m, 1 H) 6.56 (s, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C21)-D01	
B00-X00-M00(C22)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 1.74 - 2.06 (m, 4 H) 2.08 (s, 3 H) 2.73 - 2.78 (m, 2 H) 2.74 - 2.86 (m, 1 H) 2.94 (t, J=7.62 Hz, 2 H) 3.28 - 3.36 (m, 1 H) 3.91 - 4.04 (m, 1 H) 4.30 (q, J=7.11 Hz, 2 H) 4.48 - 4.59 (m, 1 H) 5.78 - 5.97 (m, 1 H) 6.61 (s, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C23)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 2.32 (s, 6 H) 2.76 (t, J=7.68 Hz, 2 H) 2.94 (t, J=7.50 Hz, 2 H) 3.34 (m, 2 H) 4.30 (q, J=7.07 Hz, 2 H) 4.61 (m, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B00-X00-M00(C24)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t,

	J=7.07 Hz, 3 H) 1.71 (m, 2 H) 2.32 (s, 6 H) 2.76 (t, J=7.68 Hz, 2 H) 2.94 (t, J=7.50 Hz, 2 H) 3.34 (m, 2 H) 4.30 (q, J=7.07 Hz, 2 H) 4.61 (m, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B10-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 3 H) 2.53-2.51 (m, 6 H) 2.97 and 2.51(2t, 4 H J 7.44 Hz) 3.13 (m, 4 H) 4.30 (m, 2 H) 6.96 (m, 2 H) 7.37 (m, 2 H) 8.37 (s, 1 H) 9.14 (s, 1 H).
B04-X00-M00(C21)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J=7.07 Hz, 3 H) 1.89 - 1.96 (m, 2 H) 2.00 - 2.15 (m, 4 H) 2.79 - 2.89 (m, 4 H) 2.98 (t, J=7.87 Hz, 2 H) 3.52 (s, 2 H) 4.32 (q, J=7.15 Hz, 2 H) 5.48 - 5.66 (m, 1 H) 6.99 - 7.09 (m, 1 H) 7.21 - 7.43 (m, 7 H) 7.59 (dd, J=8.60, 1.04 Hz, 2 H) 8.43 (s, 1 H) 9.45 (s, 1 H)
B10-X00-M04(C15)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.26 (m, 7 H) 2.98 (m, 6 H) 3.33 (m, 2 H) 4.30 (q, 2 H) 6.32 (s, 2 H) 6.70 (d, 2 H) 7.33 (d, 2 H) 7.39 (m, 1 H) 7.47 (m, 2 H) 7.67 (m, 3 H) 8.42 (m, 1 H) 9.29 (m, 1 H)
B10-X00-M00(C15)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, 3 H) 2.30 (m, 4 H) 2.52 (m, 5 H) 2.86 (m, 2 H) 3.07 (m, 4 H) 4.33 (q, 2 H) 6.03 (s, 1 H) 6.88 (d, 2 H) 7.39 (m, 1 H) 7.51 (m, 2 H) 7.65 (m, 5 H) 8.36 (s, 1 H) 9.42 (s, 1 H)

Example 17

Step 8. Ethyl 8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B13-X00-M03(C01)-D01]



A solution of ethyl 6-[(dimethylamino)methylene]-1,4,4-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (0.50 g, 1.6 mmol) and N-[3-chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-guanidine (0.48 g, 1.8 mmol) in anhydrous dimethylformamide was heated to 100°C and kept at this temperature for 37 hours. After cooling, the mixture was diluted with water (50 mL) and the resulting precipitate was collected by filtration and dried to give the title compound (0.72 g, 85% yield) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.75 (s, 2 H) 2.84 (s, 3 H) 3.33 (m, 8 H) 4.32 (q, *J* 7.07 Hz, 2 H) 4.37 (s, 3 H) 7.20 (d, *J* 8.78 Hz, 1 H) 7.57 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.01 (d, *J* 2.44 Hz, 1 H) 8.44 (s, 1 H) 9.68 (s, 1 H).

By working according to this methodology, and by taking into account that when the guanidine derivative is available as a salt, stoichiometric amounts of potassium carbonate were employed, the following compounds were prepared:

Ethyl 1,4,4-trimethyl-8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B12-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 1.34 (s, 6 H) 2.24 (s, 3 H) 2.46 (s, 4 H) 2.75 (s, 2 H) 2.84 (t, *J* 4.63 Hz, 4 H) 4.32 (q, *J* 7 11 Hz, 2 H) 4.34 (s, 3 H) 7.54 (d, *J* 8 78 Hz, 1 H) 7.93 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.06 (d, *J* 2.44 Hz, 1 H) 8.45 (s, 1 H) 9.78 (s, 1 H);

Ethyl 8-anilino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.74 (s, 2 H) 4.32 (q, *J* 7.15 Hz, 2 H) 4.36 (s, 3 H) 6.98 (tt, *J* 7.36, 1.07, 1.04 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.38 Hz, 2 H) 7.71 (dd, *J* 8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.54 (s, 1 H);

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1 H- pyrazolo[4,3-h]quinazoline-3-carboxylate [B10-X00-M03(C01)-D01]

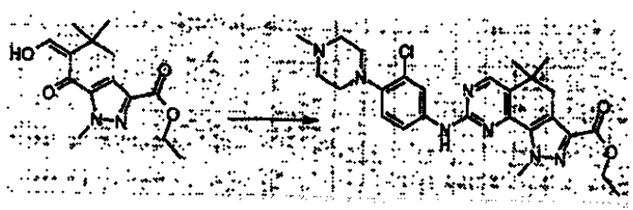
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.71 (s, 2 H) 3.03 - 3.15 (m, 4 H) 4.32 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 9.28 (s, 1 H);

Ethyl 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.31 (s, 6 H) 2.64 (s, 2 H) 4.31 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.61 (s, 2 H) 8.18 (s, 1 H).

Example 18

Ethyl 8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-1,5,5-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B13-X00-M02(C01)-D01]



A solution of ethyl 6-(hydroxymethylene)-1,5,5-trimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (400 mg, 1.44 mmol) and N-[3-chloro-4-(4-methyl-piperazin-1-yl)-phenyl]-guanidine (424 mg, 1.58 mmol) in anhydrous dimethylformamide (5 mL) was heated at 100°C for 3 hours. After cooling, the reaction mixture was poured into brine (50 mL) and extracted with ethyl acetate (50 mL x 2). The extracts were collected, dried on Na_2SO_4 and evaporated to dryness. The crude material was purified by flash chromatography on silica gel eluted with dichloromethane/methanol 9:1 to give the pure title compound (240 mg, 33% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.92 (s, 2 H) 2.95 (t, *J* 4.63 Hz, 4 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.39 (s, 3 H) 7.14 (d, *J* 8.78 Hz, 1 H) 7.52 (dd, *J* 8.78, 2.44 Hz, 1 H) 7.98 (d, *J* 2.44 Hz, 1 H) 8.54 (s, 1 H) 9.63 (s, 1 H).

By working according to this methodology, and by taking into account that when the guanidine derivative is available as a salt, stoichiometric amounts of potassium carbonate were employed, the following compounds were prepared:

Ethyl 1,5,5-trimethyl-8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B12-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.86 (t, *J* 4.51 Hz, 4 H) 2.93 (s, 2 H) 4.32 (q, *J* 7.15 Hz, 2 H) 4.37 (s, 3 H) 7.54 (d, *J* 8.66 Hz, 1 H) 7.93 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.09 (d, *J* 2.44 Hz, 1 H) 8.56 (s, 1 H) 9.81 (s, 1 H);

Ethyl 8-anilino-1,5,5-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.93 (s, 2 H) 4.31 (q, *J* 7.15 Hz, 2 H) 4.38 (s, 3 H) 6.98 (tt, *J* 7.36, 1.07, 1.04 Hz, 1 H) 7.32 (dd, *J* 8.47, 7.50 Hz, 2 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.53 (s, 1 H) 9.57 (s, 1 H);

Ethyl 1,5,5-trimethyl-8-{[4-(4-methylpiperazin-1-yl)-phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B10-X00-M02(C01)-D01]

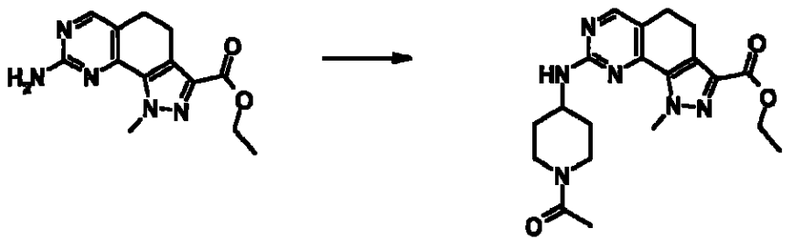
^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.30 (s, 6 H) 1.34 (t, *J*=7.07 Hz, 3 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.91 (s, 2 H) 3.09 (m, 4 H) 4.31 (q, *J*=7.19 Hz, 2 H) 4.35 (s, 3 H) 6.92 (d, *J*=9.29 Hz, 2 H) 7.52 (d, *J*=9.29 Hz, 2 H) 8.46 (s, 1 H) 9.30 (s, 1 H);

Ethyl 1,5,5-trimethyl-8-amino-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (s, 6 H) 1.32 (t, *J*=7.13 Hz, 3 H) 2.86 (s, 2 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.35 (s, 3 H) 6.61 (s, 2 H) 8.29 (s, 1 H).

Example 19

Ethyl 8-(1-acetyl-piperidin-4-yl)amino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B91-X00-M00(C01)-D01]



To a suspension of 5.187 g (19 mmol) of ethyl 8-amino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in dry dimethylformamide (120 mL), were added 1-acetyl-4-piperidone (4.7 mL, 38 mmol), CF_3COOH (10 mL, 128 mmol) and $NaBH(OAc)_3$ (8.862 g, 42 mmol). After 18 hours, NaOH 0.33N (800 mL, 264 mmol) was added dropwise to the mixture. The precipitate was filtered, washed with water and dried in oven to dryness to give 5.3 g (70 % yield) of the title compound.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.34 (t, *J* 7.07 Hz, 3 H) 1.47 (m, 2 H) 1.95 (m, 2 H) 2.02 (s, 3 H) 2.73 (m, 1 H) 2.77 (m, 2 H) 3.17 (m, 1 H) 3.83 (m, 1 H) 3.95 (m, 1 H) 4.30 (q, *J* 7.07 Hz, 2 H) 4.31 (m, 1 H) 4.33 (s, 3 H) 7.14 (m, 1 H) 8.24 (s, 1 H)

By working according to the above method the following compounds were prepared:

Table VIII

B73-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.13 Hz, 3 H) 1.54 (m, 4 H) 1.70 (m, 2 H) 1.94 (m, 2 H) 2.77 (m, 2 H) 2.94 (t, *J* 7.74 Hz, 2 H) 4.17 (m, 1 H) 4.30 (q, *J* 7.07 Hz, 2 H) 4.35 (s, 3 H) 7.11 (d, *J* 6.34 Hz, 1 H) 8.22 (s, 1 H)
B89-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.32 (t, *J* 7.13 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99 Hz, 2 H) 2.89 (m, 6 H) 3.94 (m, 3

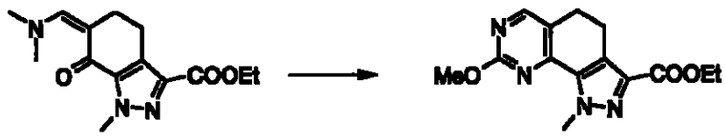
	H) 4.05 (q, *J* 7.07 Hz, 2 H) 4.30 (q, *J* 7.19 Hz, 2 H) 4.33 (s, 3 H) 7.13 (d, *J* 5.85 Hz, 1 H) 8.24 (s, 1 H)
B27-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.37 (m, 5 H) 1.32 (t, *J*=7.07 Hz, 3 H) 1.53 - 1.99 (m, 5 H) 2.76 (t, *J*=7.62 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.62 - 3.77 (m, 1 H) 4.30 (q, *J*=7.15 Hz, 2 H) 4.34 (s, 3 H) 6.98 (d, *J*=5.37 Hz, 1 H) 8.21 (s, 1 H)
B90-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.54 (m, 2 H) 1.89 (d, *J*=12.80 Hz, 2 H) 1.96 (m, 2 H) 2.18 (s, 3 H) 2.77 (m, 4 H) 2.94 (t, *J*=7.74 Hz, 2 H) 3.66 (m, 1 H) 4.30 (q, *J*=7.19 Hz, 2 H) 4.33 (s, 3 H) 7.03 (d, *J*=6.46 Hz, 1 H) 8.22 (s, 1 H)
B94-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, J=7.2 Hz, 3 H); 1.58 (m, 2 H); 1.98 (m, 2 H); 2.75 (m, 2 H); 2.92 (m, 2 H); 3.30 (m, 2 H); 3.59 (m, 2 H); 3.72 (m, 1 H); 4.26 (s, 3 H); 4.29 (q, J=7.2 Hz, 2 H); 7.13 (d, J=7.2 Hz, 1 H); 7.68 (m, 2 H); 7.75 (m, 1 H); 7.78 (m, 2 H); 8.20 (s, 1 H)
B100-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.2 Hz, 3 H); 1.45 (m, 2 H); 1.90 (m, 2 H); 2.19 (m, 3 H); 2.31 (m, 4 H); 2.77(m, 2 H); 2.87(m, 2 H), 2.94 (m, 2 H); 3.15(m, 4 H); 3.60 (m, 2 H); 3.87 (m, 1 H); 4.30 (q, J=7.2 Hz, 2 H); 4.33 (s, 3 H), 7.13 (bs, 1 H); 8.23 (s, 1 H)
B73-X00-M00(C09)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 - 1.24 (m, 4 H) 1.34 (t, *J*=7.13 Hz, 3 H) 1.40 - 1.62 (m, 4 H) 2.83 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.44 Hz, 2 H) 3.83 (s, 3 H) 3.85 - 3.87 (m, 1 H) 4.34 (q, *J*=7.15 Hz, 2 H) 6.94 (s, 1 H) 7.05 (d, *J*=8.90 Hz, 2 H) 7.46 (d, *J*=9.02 Hz, 2 H) 8.18 (s, 1 H)
B73-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.67 (m, 8 H) 1.34 (t, *J*=7.13 Hz, 3 H) 2.85 (t, *J*=7.68 Hz, 2 H) 3.03 (t, *J*=7.68 Hz, 2 H) 3.28 - 3.44 (m, 1 H) 4.35 (q, *J*=7.07 Hz, 2 H) 6.93 (s, 1 H) 7.82 (d, *J*=8.78 Hz, 2 H) 8.04 (d, *J*=8.66 Hz, 2 H) 8.22 (s, 1 H)
B73-X00-M00(C08)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.54 (m, 8 H) 1.34 (t, *J*=7.13 Hz, 3 H) 2.85 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.44 Hz, 2 H) 3.25 - 3.42 (m, 1 H) 4.30 - 4.41 (m, *J*=7.07, 7.07, 7.07 Hz, 2 H) 6.87 (s, 1 H) 7.48 (s, 2 H) 7.79 (d, *J*=8.78 Hz, 2 H) 7.95 (d, *J*=8.78 Hz, 2 H) 8.22 (s, 1 H)
B73-X00-M00(C11)-D01	
B73-X00-M00-(C19)-D01	
B91-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J = 7.08) 2.04 (s, 3 H) 2.75 and 2.94 (2t, 4 H, J =7.32) 4.31 (q, 2 H, J = 7.08) 8.26 (s, 1 H)

B73-X00-M00 (C20)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.35 (m, 3 H) 1.50 - 1.63 (m, 4 H) 1.66 - 2.17 (m, 8 H) 2.72 - 2.86 (m, 1 H) 2.76 - 2.81 (m, 2 H) 2.94 (t, *J*=7.74 Hz, 2 H) 3.11 - 3.27 (m, 1 H) 3.86 - 3.97 (m, 1 H) 4.12 - 4.23 (m, 1 H) 4.30 (q, *J*=7.15 Hz, 2 H) 4.34 - 4.44 (m, 1 H) 5.82 - 5.98 (m, 1 H) 7.14 (s, 1 H) 8.08 (s, 1 H) 8.24 (s, 1 H)
B73-X00-M00(C22)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3H, J=7.07) 2.09 (s, 3H) 2.94 and 2.76 (2t, 4H, J=7.68) 3.18 (m, 1H) 4.02 (m, 1H) 4.18 (m, 1H) 4.30 (q, 2H, J=7.07 Hz) 4.56 (m, 1H) 5.88 (m, 1H) 7.13 (bs, 1H) 8.24 (s, 1H)
B91-X00-M00(C22)-D01	
B73-X00-M00(C023)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.32 (s, 6 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.34 (m, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.61 (m, 2 H) 8.20 (s, 1 H)
B73-X00-M00(C024)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.29 (s, 6 H) 2.50 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.54 (m, 2 H) 8.20 (s, 1 H)
B95-X00-M00(C01)-D01	
B91-X00-M03(C01)-D01	^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.31 (s, 6 H) 1.32 (t, *J*=7.07 Hz, 3 H) 1.49 (m, 2 H) 1.96 (m, 2 H) 2.02 (s, 3 H) 2.65 (s, 2 H) 2.76 (m, 1 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.95 (m, 1 H) 4.30 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 7.17 (s, 1 H) 8.24 (s, 1 H)
B89-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 1.35 (t, *J*=7.14 Hz, 3 H) 1.43 (m, 2 H) 1.95 (dd, *J*=12.43, 2.54 Hz, 2 H) 2.67 (s, 2 H) 2.98 (m, 2 H) 3.92 (m, 1 H) 3.99 (m, 2 H) 4.08 (q, *J*=7.00 Hz, 2 H) 4.33 (q, *J*=7.10 Hz, 2 H) 4.34 (s, 3 H) 7.17 (s, 1 H) 8.25 (s, 1
B73-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 1.32 (t, *J*=7.13 Hz, 3 H) 1.55 (m, 4 H) 1.70 (m, 2 H) 1.94 (m, 2 H) 2.64 (s, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.11 Hz, 2 H) 4.34 (s, 3 H) 7.12 (d, *J*=7.19 Hz, 1 H) 8.21 (s, 1 H)
B92-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.31 (s, 6 H) 1.46 (m, 2 H) 1.96 (m, 2 H) 2.65 (s, 2 H) 3.18 (m, 2 H) 3.62 (m, 1 H) 4.01 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 4.40 (m, 1 H) 7.18 (s, 1 H) 7.34 - 7.49 (m, 5 H) 8.23 (s, 1 H)

B93-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.31 (t, *J*=7.19 Hz, 3 H) 1.59 (m, 2 H) 2.01 (m, 2 H) 2.89 (s, 3 H) 2.90 (m, 2 H) 3.56 (m, 2 H) 3.87 (m, 1 H) 4.30 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 8.24 (s, 1 H)
B94-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.31 (t, *J*=7.19 Hz, 3 H) 1.59 (m, 2 H) 1.99 (m, 2 H) 2.56 (m, 2 H) 2.63 (s, 2 H) 3.59 (m, 2 H) 3.73 (m, 1 H) 4.25 (s, 3 H) 4.30 (q, *J*=7.03 Hz, 2 H) 7.14 (d, *J*=6.83 Hz, 1 H) 7.68 (m, 2 H) 7.73 (m, 1 H) 7.77 (m, 2 H) 8.19 (s, 1 H)
B91-X00-M05	^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.37 (m, 2 H) 1.89 (m, 2 H) 2.02 (s, 3 H) 2.75 (m, 1 H) 2.93 (m, 2 H) 3.17 (m, 1 H) 3.64 (m, 2 H) 3.81 (m, 1 H) 4.01 (m, 1 H) 4.26 (m, 1 H) 4.36 (m, 2 H) 6.54 (bs, 1 H) 7.17 (s, 1 H) 8.23 (s, 1 H)

Example 20

Ethyl 8-methoxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B67-X03-M00(C01)-D01]

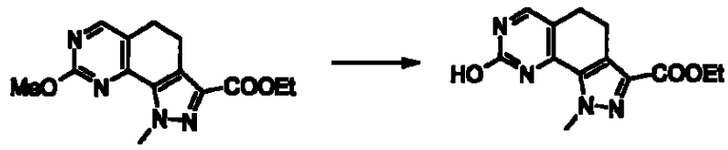


2.0 g (7.2 mmol) of ethyl 6-[(dimethylamino)methylene]-1-methyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 200 mL of acetonitrile and 17.4 g (70.6 mmol) of methylisourea sulfate and 10.0 g (72.4 mmol) of potassium carbonate were added. The reaction mixture was stirred at reflux for 16 hours. The solvent was then evaporated, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. After a chromatography on a silica gel column (eluant dichloromethane) 1.7 g of product were obtained (86% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.98 (m, 4 H) 3.97 (s, 3 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.34 (s, 3 H) 8.54 (s, 1 H).

Example 21

Ethyl 8-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X03-M00(C01)-D01]

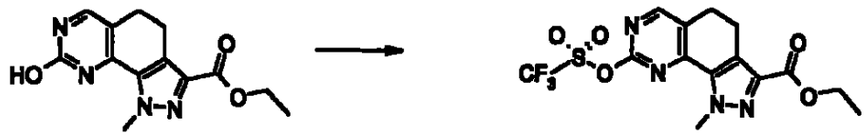


1.5 g (5.2 mmol) of ethyl 8-methoxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in 90 mL of acetonitrile and 1.6 g (10.6 mmol) of sodium iodide and 1.5 mL of trimethylsilylchloride were added. After a day under stirring and nitrogen atmosphere at room temperature the solvent was evaporated, the residue redissolved with a mixture dichloromethane/methanol 4/1 and washed with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue crystallized from methanol leading 1.1 g of the title compound (78% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.07 Hz, 3 H) 2.84 (m, 4 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.29 (s, 3 H) 7.87 (s, 1 H) 11.70 (s, 1 H).

Example 22

Ethyl 1-methyl-8-{[(trifluoromethyl)sulfonyl]oxy}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B66-X03-M00(C01)-D01]

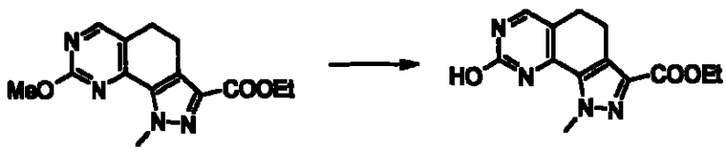


0.60 g (2.19 mmol) of ethyl 8-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate and 0.31 mL (2.19 mmol) of triethylamine were dissolved in 60 mL of dichloromethane and stirred for 5 hours at –78°C; then, 0.72 mL (2.19 mmol) of triflic anhydride were added. The reaction was stirred overnight and allowed to come to room temperature, washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness. The residue was triturated with diethyl ether/acetone and the product collected by filtration giving 0.60 g (67% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 3.09 (s, 4 H) 4.28 (s, 3 H) 4.32 (q, *J* 7.11 Hz, 2 H) 8.86 (s, 1 H).

Example 23

Ethyl 8-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B97-X00-M00(C01)-D01]



1.5 g (5.2 mmol) of ethyl 8-methoxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in 90 mL of acetonitrile and 1.6 g (10.6 mmol) of sodium iodide and 1.5 mL of trimethylsilylchloride were added. After a day under stirring and nitrogen atmosphere at room temperature the solvent was evaporated, the residue redissolved with a mixture dichloromethane/methanol 4/1 and washed with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue crystallized from methanol leading 1.1 g of the title compound (78% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.07 Hz, 3 H) 2.84 (m, 4 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.29 (s, 3 H) 7.87 (s, 1 H) 11.70 (s, 1 H).

Example 22

Ethyl 1-methyl-8-{[(trifluoromethyl)sulfonyl]oxy}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B66-X03-M00(C01)-D01]

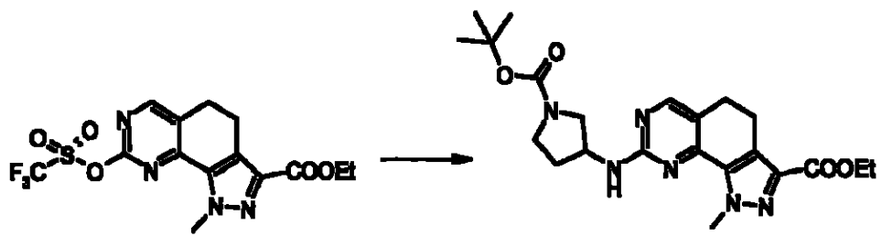


0.60 g (2.19 mmol) of ethyl 8-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate and 0.31 mL (2.19 mmol) of triethylamine were dissolved in 60 mL of dichloromethane and stirred for 5 hours at –78°C; then, 0.72 mL (2.19 mmol) of triflic anhydride were added. The reaction was stirred overnight and allowed to come to room temperature, washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated to dryness. The residue was triturated with diethyl ether/acetone and the product collected by filtration giving 0.60 g (67% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 3.09 (s, 4 H) 4.28 (s, 3 H) 4.32 (q, *J* 7.11 Hz, 2 H) 8.86 (s, 1 H).

Example 23

Ethyl 8-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B97-X00-M00(C01)-D01]



To a solution of 1.5 g (3.7 mmol) of ethyl 1-methyl-8-{[(trifluoromethyl)sulfonyl]oxy}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in 150 mL of anhydrous dioxane, 756 mg (4.1 mmol) of tert-butyl 3-aminopyrrolidine-1-carboxylate were added. The reaction mixture was stirred at room temperature overnight. The solvent was then removed under reduced pressure, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over sodium sulfate and evaporated. 1.2 g (88 % yield) of the title compound was collected by filtration after trituration with diethylether.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.38 - 1.44 (m, 9 H) 1.81 - 1.99 (m, 1 H) 2.09 - 2.23 (m, 1 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.80 Hz, 2 H) 3.13 - 3.66 (m, 4 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.32 - 4.41 (m, 1 H) 4.34 (s, 3 H) 7.40 (s, 1 H) 8.27 (s, 1 H)

Analogously, but employing the suitable amino derivative, the following compounds was prepared:

ethyl 8-[(1-benzylpyrrolidin-3-yl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B98-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.07 Hz) 2.21 and 1.79 (2m, 2 H) 2.51 and 2.69 (2m, 4 H) 2.93 and 2.74 (2t, 4 H, J 7.68 Hz) 4.30 (m, 5 H) 7.33 (m, 6 H) 8.23 (s, 1 H).

Example 24

8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B00-X00-M00(C01)-D03]



2.5 g of ethyl 8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (9.16 mmol) were dissolved in 40 mL of methanol, 40 mL of dimethylformamide and 50 mL of NH_4OH 30 % mixture. The mixture was maintained at 65°C under stirring for a day. The solvent was then evaporated to dryness, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The crude was triturated with diethyl ether and the product collected by filtration (50 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.68 and 2.90 (2m, 4 H) 4.28 (s, 3 H) 6.50 (bs, 2 H) 7.13-7.42 (bs, 2 H) 8.15 (s, 1 H).

By working according to this method, the following compounds were prepared:

Table IX

B04-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 2.96 (m, 2 H) 4.31 (s, 3 H) 6.94 (m, 1 H) 7.22 (bs, 1 H) 7.28 (m, 2 H) 7.68 (m, 2 H) 8.88 (s, 1 H) 9.48 (bs, 1 H).
B06-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (m, 2 H) 2.97 (m, 2 H) 4.33 (s, 3 H) 6.97 (m, 1 H) 7.29 (m, 1 H) 7.44 (bs, 1 H) 7.66 (m, 1 H) 7.98 (m, 1 H) 8.43 (s, 1 H) 9.73 (bs, 1 H).
B07-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (t, *J* 7.68 Hz, 2 H) 2.98 (t, *J* 7.74 Hz, 2 H) 4.30 (s, 3 H) 7.24 (s, 1 H) 7.26 (dd, *J* 8.66, 0.85 Hz, 1 H) 7.44 (s, 1 H) 7.51 (t, *J* 7.93 Hz, 1 H) 7.90 (d, *J* 8.05 Hz, 1 H) 8.19 (s, 1 H) 8.45 (s, 1 H) 9.87 (s, 1 H)
B08-X00-M00(C01)-D03	
B09-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.97 (m, 2 H) 4.31 (s, 3 H) 6.58 (m, 1 H) 7.00-7.40 (3m, 4 H) 8.37 (s, 1 H) 9.32 (bs, 1 H).
B10-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.64 (s, 3 H) 2.76 (m, 2 H) 2.95 (m, 2 H) 4.29 (s, 3 H) 6.92 (m, 2 H) 7.23 (bs, 1 H) 7.41 (bs, 1 H) 7.54 (m, 2 H) 8.32 (s, 1 H) 9.27 (bs, 1 H).
B36-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (m, 2 H) 2.95 (m, 2 H) 4.28 (s, 3 H) 5.95 (s, 2 H) 6.84 (m, 1 H) 7.06 (m, 1 H) 7.34 (m, 1 H) 7.22 (bs, 1 H) 7.42 (bs, 1 H) 8.34 (s, 1 H) 9.34 (bs, 1 H).
B04-X00-M00(C02)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.77 (s, 9H) 2.72 (m, 2 H) 2.96 (m, 2 H) 7.02 (m, 1 H) 7.20-7.40 (m, 3 H) 7.65 (m, 1 H) 7.67 (m, 1 H) 8.40 (s, 1 H) 9.21 (bs, 1 H).
B04-X00-M00(C04)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (t, *J* 7.68 Hz, 2 H) 2.96 (t, *J* 7.74 Hz, 2 H) 3.83 (q, *J* 5.69

	Hz, 2 H) 4.78 (t, *J* 5.49 Hz, 1 H) 4.84 (t, *J* 5.79 Hz, 2 H) 6.94 (t, *J* 7.38 Hz, 1 H) 7.23 (s, 1 H) 7.28 (m, 2 H) 7.43 (s, 1 H) 7.67 (d, *J* 7.68 Hz, 2 H) 8.37 (s, 1 H) 9.42 (s, 1 H)
B04-X00-M00(C07)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (m, 4 H) 5.47 (s, 2 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (t, 4 H) 7.49 (s, 1 H) 7.65 (t, *J* 7.68 Hz, 3 H) 8.41 (s, 1 H) 9.48 (s, 1 H)
B04-X00-M00(C08)-D03	
B04-X00-M00(C09)-D03	
B04-X00-M00(C10)-D03	
B04-X00-M00(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (m, 2 H) 2.92 (m, 2 H) 5.44 (q, *J* 9.02, 2 H) 6.90 (m, 1 H) 7.24 (m, 2 H) 7.80 (m, 3 H) 7.93 (bs, 1 H) 8.40 (s, 1 H) 9.72 (bs, 1 H).
B04-X00-M04(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 3.00 (m, 2 H) 5.75 (q; *J* 8.90 Hz, 2 H) 6.97 (m, 1 H) 7.28 (m, 2 H) 7.40 (bs, 1 H) 7.56 (m, 2 H) 8.42 (s, 1 H) 9.56 (bs, 1 H)
B04-X00-M00(C11)-D03	
B04-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (m, 2 H) 3.03 (m, 2 H) 6.95 (m, 1 H) 7.30 (m, 3 H) 7.51 (bs, 1 H) 7.89 (m, 2 H) 8.40 (s, 1 H) 9.45 (bs, 1 H) 14.03 (bs, 1 H).
B12-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.90 (m, 8 H) 4.33 (s, 3 H) 7.27 (s, 1 H) 7.47 (s, 1 H) 7.53 (d, *J* 8.78 Hz, 1 H) 7.93 (dd, *J* 8.90, 2.44 Hz, 1 H) 8.08 (d, *J* 2.56 Hz, 1 H) 8.45 (s, 1 H) 9.76 (s, 1 H)
B13-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.92 (m, 8 H) 4.35 (s, 3 H) 7.14 (d, *J* 8.78 Hz, 1 H) 7.27 (s, 1 H) 7.47 (s, 1 H) 7.53 (dd, *J*=8.78, 2.44 Hz, 1 H) 7.97 (d, *J*=2.56 Hz, 1 H) 8.42 (s, 1 H) 9.58 (s, 1 H)
B27-X00-M00(C03)-D03	
B27-X00-M04(C03)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (s, 3 H) 1.64 (m, 2 H) 4.85 (m, 2 H) 6.67 (m, 1 H) 7.16-7.24 (m, 3 H) 7.25-7.42 (2 bs, 2 H) 9.25 (bs, 1 H).

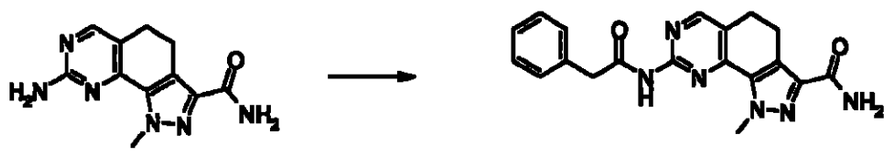
B04-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 (dd, *J*=11.58, 4.15 Hz, 2 H) 2.01 - 2.10 (m, 2 H) 2.12 - 2.23 (m, 2 H) 2.80 (t, *J*=7.56 Hz, 2 H) 2.88 (d, *J*=11.10 Hz, 2 H) 2.98 (t, *J*=7.50 Hz, 2 H) 3.52 (s, 2 H) 5.48 - 5.61 (m, 1 H) 6.99 - 7.07 (m, 1 H) 7.26 (s, 1 H) 7.27 - 7.39 (m, 7 H) 7.43 (s, 1 H) 7.60 (dd, *J*=8.54, 1.10 Hz, 2 H) 8.41 (s, 1 H) 9.43 (s, 1 H)
B00-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (d, *J*=11.95 Hz, 2 H) 2.10 - 2.33 (m, 4 H) 2.70 (t, *J*=7.74 Hz, 2 H) 2.93 (t, *J*=7.56 Hz, 4 H) 3.55 (s, 2 H) 5.41 - 5.69 (m, 1 H) 6.51 (s, 2 H) 7.15 - 7.43 (m, 7 H) 8.17 (s, 1 H)
B10-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (m, 4 H) 2.79 (m, 4 H) 3.13 (m, 4 H) 5.46 (m, 1 H) 6.95 (m, 2 H) 7.38 (m, 2 H) 7.36 and 7.26 (2s, 2 H) 8.34 (s, 1 H) 9.12 (s, 1 H).
B04-X00-M04(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (t, *J*=7.68 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 4.34 (s, 3 H) 6.92 - 7.03 (m, 1 H) 7.26 (s, 1 H) 7.31 (dd, *J*=8.41, 7.44 Hz, 2 H) 7.47 (s, 1 H) 7.72 (dd, *J*=8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B73-X00-M00(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 - 1.78 (m, 6 H) 1.84 - 2.00 (m, 2 H) 2.78 (t, *J*=7.74 Hz, 2 H) 2.98 (t, *J*=7.74 Hz, 2 H) 4.02 - 4.20 (m, 1 H) 5.81 (q, *J*=8.82 Hz, 2 H) 7.22 (d, *J*=6.95 Hz, 1 H) 7.41 (s, 1 H) 7.45 (s, 1 H) 8.25 (s, 1 H)
B73-X00-M00(C04)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 - 1.77 (m, 6 H) 1.84 - 2.01 (m, 2 H) 2.73 (t, *J*=7.74 Hz, 2 H) 2.95 (t, *J*=7.56 Hz, 2 H) 3.85 (t, *J*=6.10 Hz, 2 H) 4.09 - 4.25 (m, 1 H) 4.73 - 4.90 (m, 1 H) 4.82 (t, *J*=6.16 Hz, 2 H) 7.04 (d, *J*=5.98 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B73-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 AND 2.94 (2T, 4 H, J 7.80 Hz) 3.55 (s, 2 H) 4.15 (m, 1 H) 5.62 (m, 1 H) 7.25-7.36 (m, 5 H) 7.23 and 7.39 (2s, 2 H) 8.20 (s, 1 H).
B97-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.4 (s, 9H) 1.8-2.2 (2m, 2 H) 2.75 and 2.96 (2t, 4 H) 3.2-3.7 (m, 4 H) 4.2-4.4 (m, 4 H) 7.38 (s, 1 H) 7.24 and 7.44 (2s, 2 H) 8.25 (s, 1 H).
B98-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.6-2.2 (m, 2 H) 2.72 (m, 4 H) 2.94 (m, 4 H) 4.27 (s, 3 H) 4.32 (m, 1 H) 7.33 (m, 6 H) 7.43 (2s, 2 H) 8.21 (s, 1 H).
B95-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.19 Hz, 3 H) 1.44 - 1.58 (m, 2 H) 1.87 - 1.94 (m, 2 H) 1.95 - 2.03 (m, 2 H) 2.35 (q, *J*=7.07 Hz, 2 H) 2.73 (t, *J*=7.56 Hz, 2 H) 2.89 (d, *J*=11.71 Hz, 2 H)

	2.94 (t, *J*=7.62 Hz, 2 H) 3.59 - 3.78 (m, 1 H) 4.30 (s, 3 H) 7.00 (d, *J*=7.93 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 and 2.94 (2t, 4 H, J 7.94 Hz) 4.20 (m, 1 H) 5.60 (m, 1 H) 7.25 (s, 1 H) 1.10 and 7.35 (2s, 2 H) 8.21 (s, 1 H).
B91-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H) 2.28 (s, 3 H) 3.18 (m, 4 H) 4.30 (m, 4 H) 5.50 (m, 1 H) 7.26 (s, 1 H) 7.10 and 7.36 (2s, 2 H) 8.24 (s, 1 H).
B91-X00-M00(C22)-D03	
B73-X00-M00(C22)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.07 (s, 3H) 2.94 and 2.72 (2t, 4H, *J*=7.93) 4.18 (m, 1H) 5.83 (m, 1H) 7.09 (s, 1H) 7.42 and 7.23 (2s, 2H) 8.22 (s, 1H
B73-X00-M00(C20)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.63 (m, 4 H) 1.66 - 2.15 (m, 8 H) 2.66 - 2.84 (m, 1 H) 2.72 (t, *J*=7.62 Hz, 2 H) 2.94 (t, *J*=7.68 Hz, 2 H) 3.08 - 3.39 (m, 1 H) 3.86 - 3.97 (m, 1 H) 4.10 - 4.25 (m, 1 H) 4.31 - 4.42 (m, 1 H) 5.77 - 5.95 (m, 1 H) 7.08 (s, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.09 (s, 1 H) 8.22 (s, 1 H)
B73-X00-M00(C16)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.64 (m, 8 H) 2.80 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.62 Hz, 2 H) 3.27 - 3.33 (m, 1 H) 6.77 (s, 1 H) 7.33 (s, 1 H) 7.44 - 7.57 (m, 5 H) 7.61 (s, 1 H) 8.17 (s, 1 H)
B73-X00-M00(C17)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.87 (m, 8 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.99 (s, 1 H) 6.07 (s, 2 H) 7.06 (d, *J*=7.44 Hz, 1 H) 7.13 - 7.35 (m, 6 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C09)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.68 (m, 8 H) 2.79 (t, *J*=7.62 Hz, 2 H) 3.02 (t, *J*=7.62 Hz, 2 H) 3.21 - 3.44 (m, 1 H) 3.82 (s, 3 H) 6.79 (d, *J*=5.85 Hz, 1 H) 7.04 (d, *J*=9.02 Hz, 2 H) 7.31 (s, 1 H) 7.46 (d, *J*=8.90 Hz, 2 H) 7.58 (s, 1 H) 8.16 (s, 1 H)
B73-X00-M00(C10)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.65 (m, 8 H) 2.82 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.68 Hz, 2 H) 3.25 - 3.44 (m, 1 H) 6.90 (s, 1 H) 7.42 (s, 1 H) 7.70 (s, 1 H) 7.84 (d, *J*=8.66 Hz, 2 H) 8.03 (d, *J*=8.78 Hz, 2 H) 8.21 (s, 1 H)
B73-X00-M00(C11)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.65 (m, 8 H) 2.82 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.68 Hz, 2 H) 3.13 - 3.62 (m, 1 H) 6.78 (s, 1 H) 7.37 (s, 1 H) 7.58 (ddd, *J*=7.53, 4.85, 1.04 Hz, 1 H) 7.65 (s, 1 H) 7.68 (dt, *J*=7.93, 0.91 Hz, 1 H) 8.04 - 8.10 (m, 1 H) 8.18 (s, 1 H) 8.57 (ddd, *J*=4.85, 1.86, 0.85 Hz, 1 H)

B73-X00-M00(C08)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.55 (m, 8 H) 2.82 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.56 Hz, 2 H) 3.26 - 3.42 (m, 1 H) 6.82 (s, 1 H) 7.41 (s, 1 H) 7.44 (s, 2 H) 7.64 (s, 1 H) 7.80 (d, *J*=8.66 Hz, 2 H) 7.93 (d, *J*=8.78 Hz, 2 H) 8.21 (s, 1 H)

Example 25

1-methyl-8-[(phenylacetyl)amino]-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B05-X01-M00(C01)-D03]



0.40 g (1.47 mmol) of 8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide were suspended in 20 mL of tetrahydrofuran and 5 mL of pyridine and 0.42 mL (3.22 mmol) of phenylacetylchloride were added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated, the residue redissolved with dichloromethane, washed with aqueous $NaHCO_3$ and then with water. After drying over anhydrous Na_2SO_4 the solvent was removed under reduced pressure and the crude purified by chromatography on a silica gel column (eluant cyclohexane/acetone) giving 0.35 mg of the title compound (60% yield).

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.62-3.02 (2m, 4 H) 3.76 (m, 2 H) 4.3 (s, 3 H) 7.00-7.50 (m, 7H) 8.50 (s, 1 H) 10.80 (bs, 1 H).

By working according to this method, the following compound was prepared:

8-(benzoylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B04-X01-M00(C01)-D03]

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.87-3.04 (2m, 4 H) 4.33 (s, 3 H) 7.20-7.46 (bs, 2 H) 7.47-7.53 (m, 3 H) 7.90-8.00 (m, 2 H) 8.60 (s, 1 H) 10.97 (m, 1 H).

Example 26

Ethyl 8-[(aminocarbonyl)amino]-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X02-M00(C01)-D01]

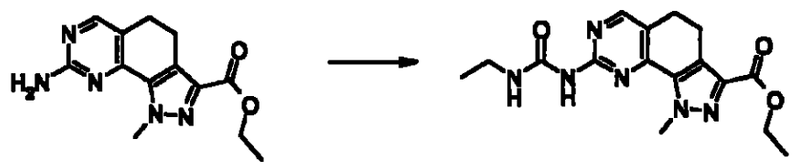


1.00 g (3.7 mmol) of ethyl 8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in 50 mL of pyridine and 1 mL (8.0 mmol) of trichloroacetylisocyanate were added. The mixture was stirred overnight at room temperature. The solvent was then evaporated under reduced pressure and the residue was treated with 50 mL of methanol. After 2 hours under stirring the solvent was removed, the residue redissolved with dichloromethane and washed with a diluted solution of ammonium hydrate. After drying over anhydrous Na_2SO_4 the organic layer was evaporated to dryness and the residue purified by chromatography on a silica gel column (eluant: dichloromethane/acetone 4/1) leading 0.40 g (34% yield) of the title compound.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.28 (t, *J* 7.07 Hz, 3 H) 2.8-3.0 (2m, 4 H) 4.19-4.34 (1s and 1q , *J* 7.07 Hz, 3 H) 7.04 (bs, 2 H) 8.44 (bs, 1 H) 9.91 (bs, 1 H).

Example 27

Ethyl 8-{[(ethylamino)carbonyl]amino}-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B03-X02-M00(C01)-D01]

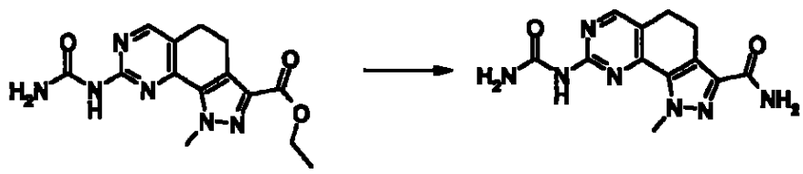


To a suspension of 18 mg (0.44 mmol) of sodium hydride 60 % in mineral oil (0.37 mmol) in dry dimethylformamide, a solution of 100 mg of ethyl 8-amino-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (0.37 mmol) in 5 mL of the same solvent was added dropwise at 0°C under stirring. After 5 minutes, 0.070 mL (0.88 mmol) of ethylisocyanate were added to the mixture and the reaction allowed to come to room temperature. After 8 hours the solvent was evaporated under reduced pressure, the residue redissolved with dichloromethane and washed with water. After drying over Na_2SO_4 the solvent was removed and the product purified by chromatography on a silica gel column (eluant dichloromethane/acetone) leading 64 mg (50 % yield) of the title compound.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.10 (t, *J* 7.20 Hz, 3 H) 1.29 (t, *J* 7.07Hz, 3 H) 2.76-3.04 (2m, 4 H) 3.12 (m, 2 H) 4.21 (q, *J* 7.07 Hz, 2 H) 4.32 (s, 3 H) 8.45 (m, 1 H) 8.71 (t, 1 H) 9.70 (bs, 1 H).

Example 28

8-[(aminocarbonyl)amino]-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B00-X02-M00(C01)-D03]



A suspension of 0.20 g (0.63 mmol) of ethyl 8-[(aminocarbonyl)amino]-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in 15 mL of a mixture methanol/dimethylformamide/ammonium hydroxide 30% 1/1/1 was stirred in a close bottle at 65°C for 48 hours. The solvent was then evaporated under reduced pressure, the residue redissolved with a mixture dichloromethane/methanol 9/1 and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The product was purified by chromatography on a silica gel column (eluant dichloromethane/acetone/methanol) giving 0.09 g (50 % yield) of the title compound.

^{1}H NMR (400 MHz), DMSO-d_6), δ ppm 2.91-3.09 (m, 4 H) 3.81 (s, 3 H) 6.47 (m, 3 H) 7.83 (bs, 2 H) 8.58 (m, 1 H).

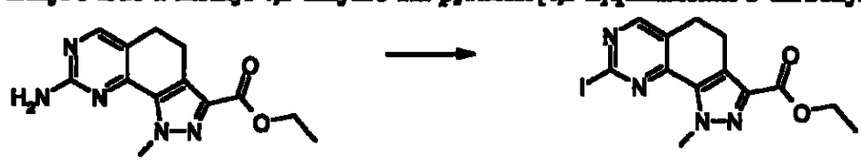
By working according to the above method, the following compound was prepared:

8-{[(ethylamino)carbonyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B03-X02-M00(C01)-D03]

^{1}H NMR (400 MHz), DMSO-d_6), δ ppm 1.10 (t, *J* 7.19 Hz, 3 H) 2.82 (t, *J* 7.62 Hz, 2 H) 2.97 (t, *J* 7.74 Hz, 2 H) 3.23 (m, 2 H) 4.28 (s, 3 H) 7.24 (s, 1 H) 7.45 (s, 1 H) 8.42 (s, 1 H) 8.75 (t, *J* 5.61 Hz, 1 H) 9.67 (s, 1 H).

Example 29

Ethyl 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate



To a well stirred, warm suspension of ethyl 8-amino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (8.8 g, 0.032 mol) in dimethoxyethane (1.2 L) maintained in an inert atmosphere of argon, cesium iodide (9.13 g, 0.035 mol), bisublimated iodine (4.45 g, 0.018 mol), copper iodide (2.01 g, 0.01 mol) and isopentyl nitrite (7.00 mL, 6.14 g, 0.052 mol) were added in sequence. The reaction mixture was stirred vigorously at 65-70°C for 18 hours. After cooling in a ice-water bath, the solid was filtered off and the filtrate was diluted with dichloromethane (2.0 L), washed with 30% ammonium hydroxide (150 mL), sodium thiosulphate (300 mL), brine and dried over anhydrous Na_2SO_4. Concentrating to a volume of about 100 mL of dimethoxyethane, the crude ethyl 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate precipitated; it was then filtered and washed with dimethoxyethane.

Flash chromatography on silica gel (eluant: dichloromethane/methanol 98:2) yielded 5.69 g of the title compound. (46% yield)

^{1}H NMR (400 MHz), DMSO-d_6), δ ppm 1.28 (t, *J* 7.07 Hz, 3 H) 2.81-3.07 (2t, *J* 8.90 Hz, 4 H) 4.24 (s, 3.H) 4.27 (q, *J* 7.07 Hz, 2 H) 8.5 (bs, 1 H).

By working according to this method, the following compounds were prepared:

ethyl 8-iodo-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 1.3 (s, 6 H) 2.8 (s, 2 H) 4.3 (s, 3 H) 4.3 (q, *J* 7.1 Hz, 2 H) 8.5 (s, 1 H);

ethyl 8-iodo-1,5,5-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

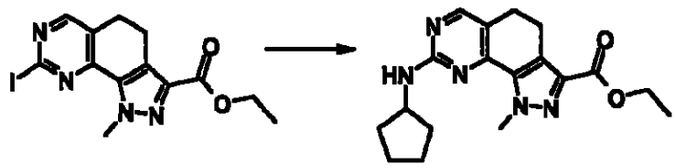
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.19 Hz, 3 H) 1.32 (s, 6 H) 2.96 (s, 2 H) 4.31 (q, *J*=7.07 Hz, 2 H) 4.28 (s, 3 H) 8.58 (s, 1 H);

ethyl 1-(3,3-dimethylbutyl)-8-iodo-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

ethyl 2-(3,3-dimethylbutyl)-8-iodo-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate.

Example 30

Ethyl 8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B73-X00-M00(C01)-D01]



Ethyl 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (0.5 g, 1.3 mmol) and cyclopentylamine (0.65 mL, 6.5 mmol) were heated at 100°C under nitrogen for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column (eluant: ethyl acetate/cyclohexane 70/30) to give 0.24 g of 8-(cyclopentylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (54% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.13 Hz, 3 H) 1.54 (m, 4 H) 1.70 (m, 2 H) 1.94 (m, 2 H) 2.77 (m, 2 H) 2.94 (t, *J* 7.74 Hz, 2 H) 4.17 (m, 1 H) 4.30 (q, *J* 7.07 Hz, 2 H) 4.35 (s, 3 H) 7.11 (d, *J* 6.34 Hz, 1 H) 8.22 (s, 1 H)

By working according to this method, the following compounds were prepared:

8-{[1-(ethoxycarbonyl)piperidin-4-yl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B89-X00-M00(C01)-D01]

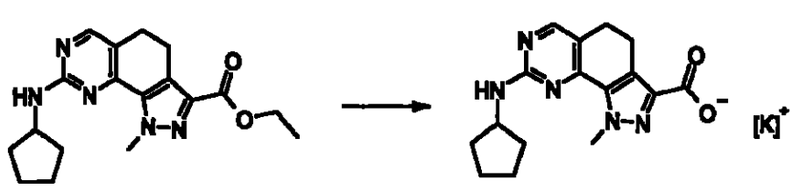
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.32 (t, *J* 7.13 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99 Hz, 2 H) 2.89 (m, 6 H) 3.94 (m, 3 H) 4.05 (q, *J* 7.07 Hz, 2 H) 4.30 (q, *J* 7.19 Hz, 2 H) 4.33 (s, 3 H) 7.13 (d, *J* 5.85 Hz, 1 H) 8.24 (s, 1 H);

B27-X00-M08(C03)-D01

B27-X00-M04(C03)-D01

Example 31

Potassium 8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B73-X00-M00(C01)-D02]



Ethyl 8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (230 mg, 0.67 mmol) was suspended in anhydrous ethanol (5 mL) and treated with a 1.5 M solution of potassium hydroxide in ethanol (1.33 mL, 3 eq.) at

reflux temperature for 1.5 hours. After cooling in ice bath, the resulting precipitate was collected by filtration to give the title compound (193 mg, 82% yield) as a crystalline solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (m, 6 H) 1.94 (m, 2 H) 2.67 (m, 2 H) 2.90 (m, 2 H) 4.16 (m, 1 H) 4.21 (s, 3 H) 6.90 (d, *J* 6.83 Hz, 1 H) 8.12 (s, 1 H)

By working according to the above method the following compounds were prepared:

Table X

B89-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99 Hz, 2 H) 2.66 (m, 4 H) 2.91 (m, 2 H) 3.94 (m, 3 H) 4.04 (q, *J* 7.07 Hz, 2 H) 4.18 (s, 3 H) 7.13 (d, 1 H, *J* 5.85 Hz, 2 H) 8.24 (s, 1 H).
B04-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 - 2.98 (m, 1 H) 6.91 - 6.97 (m, 1 H) 7.25 - 7.30 (m, 1 H) 7.66 - 7.71 (m, 1 H)
B04-X00-M04(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, *J*=7.62 Hz, 2 H) 2.95 (t, *J*=7.68 Hz, 2 H) 4.23 (s, 3 H) 6.95 (tt, *J*=7.35, 1.13 Hz, 1 H) 7.30 (dd, *J*=8.60, 7.38 Hz, 2 H) 7.73 (dd, *J*=8.72, 1.04 Hz, 2 H) 8.32 (s, 1 H) 9.39 (s, 1 H)
B91-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (m, 2 H) 1.92 (m, 2 H) 2.02 (s, 3 H) 2.67 (m, 1 H) 2.75 (m, 1 H) 2.90 (m, 2 H) 3.16 (m, 1 H) 3.82 (m, 1 H) 3.94 (m, 1 H) 4.19 (s, 3 H) 4.28 (m, 1 H) 6.94 (m, 1 H) 8.14 (s, 1 H)
B94-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 (m, 2 H) 1.99 (m, 2 H) 2.55 (m, 2 H) 2.63 (m, 2 H) 2.88 (m, 2 H) 3.58 (m, 2 H) 3.70 (m, 1 H) 4.11 (s, 3 H) 6.92 (d, *J*=6.95 Hz, 1 H) 7.68 (t, *J*=7.32 Hz, 2 H) 7.72 - 7.76 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.09 (s, 1 H)
B94-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.59 (m, 2 H) 1.99 (m, 2 H) 2.56 (m, 2 H) 3.58 (m, 2 H) 3.70 (m, 1 H) 4.08 (s, 3 H) 6.93 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.08 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D02	
B73-X00-M00(C04)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.99 (m, 8 H) 2.75 (t, *J*=7.68 Hz, 2 H) 2.93 (t, *J*=7.50 Hz, 2 H) 3.83 (t, 2 H) 4.10 - 4.22 (m, 1 H) 4.77 - 4.87 (m, 3 H) 7.04 (d, *J*=5.97 Hz, 1 H) 8.21 (s, 1 H) 12.61 (s, 1 H)
B90-X00-M00(C01)-D02	
B00-X00-M00(C21)-D02	
B04-X00-M00(C21)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 - 1.90 (m, 2 H) 2.00 - 2.20 (m, 4 H) 2.72 (t, *J*=7.68 Hz, 2 H) 2.88 (d,

	J=10.00 Hz, 2 H) 2.94 (t, J=7.50 Hz, 2 H) 3.53 (s, 2 H) 5.40 - 5.54 (m, 1 H) 6.96 - 7.04 (m, 1 H) 7.21 - 7.39 (m, 5 H) 7.26 - 7.31 (m, 2 H) 7.62 (dd, J=8.54, 0.98 Hz, 2 H) 8.32 (s, 1 H) 9.31 (s, 1 H)
B10-X00-M00(C19)-D02	

Example 32

8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B73-X00-M00(C01)-D03]



A suspension of potassium 8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (180 mg, 0.51 mmol) in anhydrous dimethylformamide (3.0 mL) and anhydrous tetrahydrofuran (3.0 mL) was treated with N-ethyl-N,N-diisopropylamine (0.175 mL, 2 eq.) and N-ethyl-N',N'-diisopropyl carbodiimide hydrochloride (EDCI) (195 mg, 2 eq). The mixture was then cooled to 0°C and treated with ammonium 1H-1,2,3-benzotriazol-1-ate (137 mg, 2 eq). After 5 minutes the reaction was warmed to room temperature and kept at this temperature overnight. The reaction was diluted with water and the resulting precipitate was collected by filtration to afford the title compound (143 mg, 90 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 4.32 (s, 3 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)

By working according to the above method the following compounds were prepared:

Table XI

B89-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99, 2 H) 2.74 (m, 2 H) 2.91 (m, 2 H) 2.95 (m, 4 H) 3.94 (m, 3 H) 4.04 (q, *J* 7.07 Hz, 2 H) 4.30 (s, 3 H) 7.09 (bs, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.22 (s, 1 H).
B91-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (m, 2 H) 1.92 (m, 2 H) 2.02 (s, 3 H), 2.74 (m, 2 H) 2.76 (m, 1 H) 2.95 (m, 2 H) 3.16 (m, 1 H) 3.81 (m, 1 H) 3.94 (m, 1 H) 4.27 (m, 1 H) 4.31 (s, 3 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.23 (s, 1 H)

B100-X00-M00(C01)-D03 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 - 1.57 (m, 2 H) 1.95 (d, *J*=12.19 Hz, 2 H) 2.74 - 2.83 (m, 5 H) 2.89 - 3.53 (m, 10 H) 3.65 (dd, *J*=12.50, 7.87 Hz, 4 H) 3.96 (t, *J*=10.61 Hz, 1 H) 4.30 (s, 3 H) 7.29 (s, 1 H) 7.47 (s, 1 H) 7.64 (s, 1 H) 8.26 (s, 1 H) 10.39 (s, 1 H)
B93-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 1.60 (m, 2 H) 2.01 (m, 2 H) 2.74 (m, 2 H) 2.89 (m, 7H,) 3.55 (m, 2 H,) 3.86 (m, 1 H) 4.31 (s, 3 H) 7.15 (bd, 1 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.24 (s, 1 H)
B92-X00-M00(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (s, 2 H) 1.99 (s, 2 H) 2.78 (t, *J*=7.56 Hz, 2 H) 2.98 (t, *J*=7.62 Hz, 2 H) 3.01 - 3.76 (m, 3 H) 4.05 (m, 1 H) 4.30 (s, 3 H) 4.41 (m, 1 H) 7.27 (s, 1 H) 7.40 (m, 2 H) 7.47 (m, 4 H) 7.60 (s, 1 H) 8.25 (s, 1 H)
B95-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.19 Hz, 3 H) 1.52 (m, 2 H) 1.90 (m, 2 H) 1.98 (m, 2 H) 2.35 (q, *J*=7.07 Hz, 2 H) 2.73 (t, *J*=7.56 Hz, 2 H) 2.89 (d, *J*=11.71 Hz, 2 H) 2.94 (t, *J*=7.62 Hz, 2 H) 3.66 (m, 1 H) 4.30 (s, 3 H) 7.00 (d, *J*=7.93 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B91-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (m,1 H); 1.46 (m, 1 H); 1.90 (m, 1 H);1.96 (m, 1 H); 2.02 (s,3 H); 2.74 (d, J=5 Hz, 3 H); 2.74 (m, 2 H); 2.75 (m, 1 H); 2.95 (m, 2 H); 3.16 (m, 1 H); 3.82 (m, 1 H); 3.95 (m,1 H); 4.29 (m, 1 H); 4.31 (s, 3 H); 7.11(bs, 1 H); 8.05 (q, J=4.5 Hz, 1 H); 8.23(s, 1 H)
B94-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.53 - 1.68 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.52 - 2.62 (m, 2 H) 2.71 (t, *J*=7.62 Hz, 2 H) 2.89 - 2.98 (m, 2 H) 3.53 - 3.63 (m, 2 H) 3.65 - 3.79 (m, 1 H) 4.24 (s, 3 H) 7.10 (d, *J*=7.32 Hz, 1 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.65 - 7.70 (m, 2 H) 7.72 - 7.78 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.19 (s, 1 H)
B73-X00-M00(C023)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.32 (s, 6 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.34 (m, 2 H) 4.17 (m, 1 H) 4.61 (m, 2 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B73-X00-M00(C024)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.29 (s, 6 H) 2.50 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 4.54 (m, 2 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B79-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.82 (m, 2

	H) 2.05 - 2.16 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.75 - 2.80 (m, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 3.01 - 3.09 (m, 2 H) 3.27 - 3.49 (m, 2 H) 3.93 - 4.10 (m, 1 H) 4.31 (s, 3 H) 7.59 (s, 1 H) 8.07 (q, *J*=4.47 Hz, 1 H) 8.26 (s, 1 H) 8.44 - 8.63 (m, 1 H) 8.69 - 8.90 (m, 1 H)
B90-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.62 (m, 2 H) 1.90 (d, *J*=13.05 Hz, 2 H) 2.00 - 2.08 (m, 2 H) 2.21 (s, 3 H) 2.70 - 2.76 (m, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 2.78 - 2.84 (m, 2 H) 2.95 (t, *J*=7.56 Hz, 2 H) 3.62 - 3.75 (m, 1 H) 4.31 (s, 3 H) 7.01 (d, *J*=7.68 Hz, 1 H) 8.06 (q, *J*=4.59 Hz, 1 H) 8.21 (s, 1 H)
B90-X00-M00(C01)-D27	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.68-2.82 (m, 4 H) 2.73 and 2.95 (2t, 4 H J 7.44 Hz) 3.67 (m, 1 H) 4.30 (s, 3 H) 7.01 (bs, 1 H) 8.11 (d, 1 H, J 4.51 Hz) 8.21 (s, 1 H)
B89-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J*=12.68, 2.68 Hz, 2 H) 2.70 - 2.79 (m, 5 H) 2.95 (t, *J*=7.68 Hz, 4 H) 3.84 - 3.99 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.30 (s, 3 H) 7.09 (d, *J*=5.98 Hz, 1 H) 8.06 (q, *J*=4.39 Hz, 1 H) 8.22 (s, 1 H)
B91-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (m, 2 H) 1.94 (m, 2 H) 2.02 (s, 3 H), 2.74 (m, 5 H) 2.96 (m, 2 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.94 (m, 1 H) 4.27 (m, 1 H) 4.31 (s, 3 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.23 (s, 1 H)
B73-X00-M00(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.73 (m, 2 H) 1.97 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.79 (t, *J*=7.62 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 4.21 (s, 1 H) 4.32 (s, 3 H) 7.68 - 7.92 (m, 1 H) 8.12 (q, *J*=4.39 Hz, 1 H) 8.24 (s, 1 H)
B100-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 - 1.51 (m, 2 H) 1.91 (dd, *J*=12.68, 3.17 Hz, 2 H) 2.21 (s, 3 H) 2.33 (s, 4 H) 2.71 - 2.76 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.82 - 2.91 (m, 2 H) 2.95 (t, *J*=7.62 Hz, 2 H) 3.12 - 3.18 (m, 4 H) 3.60 (dt, *J*=13.32, 3.34 Hz, 2 H) 3.80 - 3.95 (m, 1 H) 4.30 (s, 3 H) 7.09 (s, 1 H) 8.06 (q, *J*=4.63 Hz, 1 H) 8.22 (s, 1 H)
B92-X00-M00(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (s, 2 H) 1.99 (s, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.78 (m, 2 H) 2.98 (t, *J*=7.68 Hz, 2 H) 3.06 - 3.79 (m, 3 H) 4.05 (m, 1 H) 4.30 (s, 3 H) 4.41 (m, 1 H) 7.37 - 7.43 (m, 2 H) 7.45 - 7.49 (m, 3 H) 7.60 (s, 1 H) 8.10 (q, *J*=4.63 Hz, 1 H) 8.25 (s, 1 H)
B93-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 1.60 (m, 2 H) 2.01 (m, 2 H) 2.74 (m, 5 H) 2.89 (m, 3 H,) 2.95 (m, 4 H) 3.56 (m, 2 H,) 3.86 (m, 1 H) 4.31 (s, 3 H) 7.15 (bd, 1 H) 8.05 (m, 1 H) 8.24 (s, 1 H)

B96-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.46 (m, 2 H) 1.42 (s, 9 H) 1.84 - 1.94 (m, 2 H) 2.71 - 2.77 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.93 (m, 4 H) 3.94(m, 3 H) 4.30 (s, 3 H) 7.09 (d, *J*=4.15 Hz, 1 H) 8.07 (m, 1 H) 8.22 (s, 1 H)
B94-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 2 H) 1.98 (m, 2 H) 2.53 - 2.61 (m, 2 H) 2.67 - 2.77 (m, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 2.93 (m, 2 H) 3.58 (d, *J*=13.90 Hz, 2 H) 3.72 (m, 1 H) 4.24 (s, 3 H) 7.10 (d, *J*=7.07 Hz, 1 H) 7.64 - 7.71 (m, 2 H) 7.72 - 7.77 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.04 (q, *J*=4.59 Hz, 1 H) 8.19 (s, 1 H)
B73-X00-M00(C01)-D26 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.72 (m, 2 H) 1.97 (m, 2 H) 2.79 (m, 2 H) 2.86 (m, 11 H) 3.01 (m, 2 H) 3.81 (s, 1 H) 4.03 (s, 1 H) 4.21 (m, 1 H) 4.33 (m, 3 H) 7.70 (m, 1 H) 8.25 (s, 1 H)
B73-X00-M00(C01)-D10 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.72 (m, 2 H) 1.96 (m, 2 H) 2.79 (m, 2 H) 2.82 (d, *J*=2.2 Hz, 3 H) 2.87 (m, 2 H) 3.0-3.7 (m, 6 H) 4.21 (m, 1 H) 4.32 (s, 3 H) 4.60 (m, 1 H) 4.80 (m, 1 H) 7.70 (m, 1 H) 8.26 (s, 1 H)
B73-X00-M00(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.94 (m, 2 H) 2.76 (m, 2 H) 2.94 (m, 2 H) 4.17 (m, 1 H) 4.22 (d, *J*=5.68 Hz, 2 H) 4.36 (s, 3 H) 7.10 (bd, 1 H) 8.22 (s, 1 H) 8.35 (t, *J*=5.68 Hz, 1 H)
B73-X00-M00(C01)-D30	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.93 (m, 2 H) 2.74 (m, 2 H) 2.96 (m, 2 H) 3.81 (d, *J*=5.68 Hz, 2 H) 4.17 (m, 1 H) 4.35 (s, 3 H) 7.07 (m, 2 H) 7.38 (bs, 1 H) 8.015 (t, *J*=5.68 Hz, 1 H)8.21 (s, 1 H)
B73-X00-M00(C01)-D05	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.61 (m, 4 H) 1.64 - 1.78 (m, 2 H) 1.87 - 2.01 (m, 2 H) 2.67 - 2.89 (m, 4 H) 3.35 (s, 3 H) 4.11 - 4.23 (m, 1 H) 4.31 (s, 3 H) 7.06 (d, *J*=6.58 Hz, 1 H) 8.20 (s, 1 H) 9.88 (s, 1 H)
B73-X00-M00(C01)-D72	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.92 (m, 2 H) 2.23 (s, 6 H) 2.52 (m, 2 H) 2.71 (m, 2 H) 2.91 (m, 4 H) 4.17 (m, 1 H) 4.37 (s, 3 H) 5.09 (m, 1 H) 7.07 (d, *J* 6.83 Hz, 1 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.20 (s, 1 H) 8.28 (m, 1 H)
B73-X00-M00(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (m, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.17 (s, 6 H) 2.45 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 4.04 (m, 1 H) 4.17 (m, 1 H) 4.32 (s, 3 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.91 (d, 1 H) 8.20 (s, 1 H)
B94-X00-M00(C01)-D72	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (m, 2 H) 1.97 (m, 2 H) 2.23 (s, 6 H) 2.52 (m, 2 H) 2.55 (m, 2 H) 2.70 (m, 2 H) 2.90 (m, 4 H) 3.56 (m, 2 H) 3.72 (m, 1 H) 4.28 (s, 3 H) 5.10 (m, 1 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.24

	(m, 1 H) 7.33 (m, 2 H) 7.40 (m, 2 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.18 (s, 1 H) 8.27 (m, 1 H)
B94-X00-M00(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (m, 3 H) 1.61 (m, 2 H) 2.00 (m, 2 H) 2.19 (s, 6 H) 2.52 (m, 2 H) 2.55 (m, 2 H) 2.72 (m, 2 H) 2.94 (m, 2 H) 3.57 (m, 2 H) 3.73 (m, 1 H) 4.10 (m, 1 H) 4.25 (s, 3 H) 7.09 (m, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.19 (s, 1 H)
B91-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.43 (m, 2 H) 1.94 (m, 2 H) 2.02 (s, 3 H) 2.62 (s, 2 H) 2.76 (m, 1 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.94 (m, 1 H) 4.28 (m, 1 H) 4.29 (s, 3 H) 7.12 (d, *J*=4.15 Hz, 1 H) 7.27 (s, 1 H) 7.53 (s, 1 H) 8.21 (s, 1 H)
B89-X00-M03(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.07 Hz, 3 H) 1.34 (s, 6 H) 1.38 - 1.49 (m, 2 H) 1.89 - 1.99 (m, 2 H) 2.65 (s, 2 H) 2.90 - 3.04 (m, 2 H) 3.90 - 4.00 (m, 3 H) 4.06 (q, *J*=7.07 Hz, 2 H) 4.29 (s, 3 H) 7.31 (s, 1 H) 7.57 (s, 1 H) 8.24 (s, 1 H) 8.41 (s, 2 H)
B73-X00-M03(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 1.51 - 1.77 (m, 6 H) 1.85 - 2.04 (m, 2 H) 2.67 (s, 2 H) 4.14 - 4.25 (m, 1 H) 4.31 (s, 3 H) 7.34 (s, 1 H) 7.60 (s, 1 H) 7.86 (s, 1 H) 8.23 (s, 1 H)
B92-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.50 (m, 2 H) 1.99 (m, 2 H) 2.62 (s, 2 H) 3.10 (m, 2 H) 3.62 (m, 1 H) 4.01 (m, 1 H) 4.29 (s, 3 H) 4.40 (m, 1 H) 7.15 (s, 1 H) 7.27 (s, 1 H) 7.38 (m, 2 H) 7.47 (m, 3 H) 7.53 (s, 1 H) 8.22 (s, 1 H)
B94-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.60 (m, 2 H) 1.99 (m, 2 H) 2.52 (s, 2 H) 2.59 (m, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.57 (m, 2 H) 3.71 (m, 1 H) 4.22 (s, 3 H) 7.11 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.11 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.60 (m, 2 H) 2.02 (m, 2 H) 2.62 (s, 2 H) 2.89 (m, 5 H) 3.55 (m, 2 H) 3.85 (m, 1 H) 4.30 (s, 3 H) 7.15 (bd, 1 H) 7.27 (s, 1 H) 7.53 (s, 1 H) 8.22 (s, 1 H)
B91-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.34 - 1.52 (m, 2 H) 1.87 - 2.00 (m, 2 H) 2.02 (s, 3 H) 2.62 (s, 2 H) 2.71 - 2.84 (m, 1 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.10 - 3.22 (m, 1 H) 3.83 (d, *J*=12.93 Hz, 1 H) 3.89 - 4.02 (m, 1 H) 4.23 - 4.35 (m, 1 H) 4.30 (s, 3 H) 7.13 (d, *J*=4.88 Hz, 1 H) 8.13 (q, *J*=4.72 Hz, 1 H) 8.22 (s, 1 H)
B73-X00-M03(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 1.50 - 1.65 (m, 4 H) 1.67 - 1.78 (m, 2 H) 1.88 - 2.08 (m, 2 H) 2.67 (s, 2 H) 2.76 (d, *J*=4.63 Hz, 3 H) 4.09 - 4.24 (m, 1 H) 4.31 (s, 3 H) 7.84 (s, 1 H) 8.20 (q, *J*=4.51 Hz, 1 H) 8.23 (s, 1 H)
B92-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H)

	1.50 (m, 2 H) 1.99 (m, 2 H) 2.62 (s, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.14 (m, 2 H) 3.63 (m, 1 H) 4.01 (m, 1 H) 4.29 (s, 3 H) 4.43 (m, 1 H) 7.15 (s, 1 H) 7.39 (m, 2 H) 7.47 (m, 3 H) 8.13 (m, 1 H) 8.22 (s, 1 H)
B94-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.60 (m, 2 H) 1.99 (m, 2 H) 2.52 (s, 2 H) 2.59 (m, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.57 (m, 2 H) 3.71 (m, 1 H) 4.22 (s, 3 H) 7.11 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.11 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.60 (m, 2 H) 2.02 (m, 2 H) 2.62 (s, 2 H) 2.75 (d, 3 H) 2.89 (m, 5 H) 3.55 (m, 2 H) 3.85 (m, 1 H) 4.30 (s, 3 H) 7.16 (bd, 1 H) 8.13 (d, 1 H) 8.22 (s, 1 H)
B89-X00-M03(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.13 Hz, 3 H) 1.33 (s, 6 H) 1.35 - 1.50 (m, 2 H) 1.93 (m, 2 H) 2.64 (s, 2 H) 2.86 - 3.06 (m, 2 H) 3.84 - 4.00 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.25 (d, *J*=5.73 Hz, 2 H) 4.33 (s, 3 H) 7.14 (s, 1 H) 8.23 (s, 1 H) 8.92 (t, *J*=5.79 Hz, 1 H)
B89-X00-M03(C01)-D138	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.13 Hz, 3 H) 1.22 (s, 6 H) 1.42 (m, 2 H) 1.94 (m, 2 H) 2.62 (s, 2 H) 3.0 (m, 5 H) 3.54 (m, 2 H) 3.63 (m, 2 H) 3.95 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 7.14 (s, 1 H) 8.23 (s, 1 H) 8.92 (t, *J*=5.79 Hz, 1 H)

In table XII below see the HPLC/Mass data for some representative compounds of the invention

Table XII

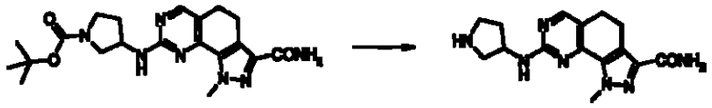
	M+H	Time	Method
B89-X00-M03(C01)-D05	444.23	2.07	2
B89-X00-M03(C01)-D31	500.29	2.6	2
B89-X00-M03(C01)-D32	500.29	2.44	2
B89-X00-M03(C01)-D33	498.24	2.85	2
B89-X00-M03(C01)-D136	541.32	1.73	2
B89-X00-M03(C01)-D137	515.3	1.79	2
B89-X00-M03(C01)-D17	555.33	1.88	2
B89-X00-M03(C01)-D76	541.32	2	2
B89-X00-M03(C01)-D78	486.28	2.29	2
B89-X00-M03(C01)-D79	516.29	1.91	2
B89-X00-M03(C01)-D14	496.3	3.16	2
B89-X00-M03(C01)-D80	486.28	2.21	2
B89-X00-M03(C01)-D44	519.28	2.49	2
B89-X00-M03(C01)-D81	539.34	1.98	2

B89-X00-M03(C01)-D12	486.28	2.55	2
B89-X00-M03(C01)-D25	467.24	2.66	2
B89-X00-M03(C01)-D82	486.28	2.27	2
B89-X00-M03(C01)-D83	530.26	2.41	2
B89-X00-M03(C01)-D84	519.28	2.66	2
B89-X00-M03(C01)-D85	487.27	2.16	2
B89-X00-M03(C01)-D60	548.29	2.63	2
B89-X00-M03(C01)-D86	499.31	1.8	2
B89-X00-M03(C01)-D87	548.29	2.94	2
B89-X00-M03(C01)-D88	510.31	3.37	2
B89-X00-M03(C01)-D89	481.26	2.51	2
B89-X00-M03(C01)-D90	504.24	3.03	2
B89-X00-M03(C01)-D91	514.27	2.82	2
B89-X00-M03(C01)-D92	498.28	2.25	2
B89-X00-M03(C01)-D93	540.32	2.49	2
B89-X00-M03(C01)-D94	474.26	2.65	2
B89-X00-M03(C01)-D04	442.25	2.48	2
B89-X00-M03(C01)-D95	502.27	2	2
B89-X00-M03(C01)-D34	548.29	2.8	2
B89-X00-M03(C01)-D96	510.24	3.09	2
B89-X00-M03(C01)-D97	486.28	2.27	2
B89-X00-M03(C01)-D45	519.28	2.52	2
B89-X00-M03(C01)-D98	500.29	2.43	2
B89-X00-M03(C01)-D99	528.29	2.86	2
B89-X00-M03(C01)-D100	526.31	2.22	2
B89-X00-M03(C01)-D06	472.26	2.15	2
B89-X00-M03(C01)-D101	514.31	2.62	2
B89-X00-M03(C01)-D102	456.26	2.67	2
B89-X00-M03(C01)-D103	512.29	2.03	2
B89-X00-M03(C01)-D104	486.28	2.27	2
B89-X00-M03(C01)-D105	512.2	2.15	2
B89-X00-M03(C01)-D106	498.31	3.22	2
B89-X00-M03(C01)-D107	512.25	2.52	2
B89-X00-M03(C01)-D108	615.33	2.98	2
B89-X00-M03(C01)-D109	561.32	3.4	2
B89-X00-M03(C01)-D110	515.27	1.99	2
B89-X00-M03(C01)-D111	528.32	2.76	2
B89-X00-M03(C01)-D112	533.29	2.76	2
B89-X00-M03(C01)-D113	512.29	2.27	2
B89-X00-M03(C01)-D114	583.33	2.9	2
B89-X00-M03(C01)-D115	525.32	1.91	2

B89-X00-M03(C01)-D116	539.34	1.95	2
B89-X00-M03(C01)-D117	514.31	2.64	2
B89-X00-M03(C01)-D118	500.29	2.52	2
B89-X00-M03(C01)-D119	502.27	2.02	2
B89-X00-M03(C01)-D120	482.28	3.06	2
B89-X00-M03(C01)-D121	553.32	2.32	2
B89-X00-M03(C01)-D122	526.31	2.38	2
B89-X00-M03(C01)-D123	498.28	2	2
B89-X00-M03(C01)-D124	456.26	2.25	2
B89-X00-M03(C01)-D125	602.26	3.64	2
B89-X00-M03(C01)-D126	584.3	3.2	2
B89-X00-M03(C01)-D127	603.33	3.08	2
B89-X00-M03(C01)-D128	565.35	1.99	2
B89-X00-M03(C01)-D129	527.34	1.91	2
B89-X00-M03(C01)-D130	541.35	1.93	2
B89-X00-M03(C01)-D131	525.32	1.78	2
B89-X00-M03(C01)-D132	616.36	2.25	2
B89-X00-M03(C01)-D133	603.33	3.37	2
B89-X00-M03(C01)-D134	521.29	3.11	2
B89-X00-M03(C01)-D135	498.28	2.03	2

Example 33

Ethyl 1-methyl-8-(pyrrolidin-3-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B99-X00-M00(C01)-D03]



A solution of 110 mg (0.27 mmol) of ethyl 8-{[1-(tert-butoxycarbonyl)pyrrolidin-3-yl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in a mixture dichoromethane-trifluoroacetic acid 9/1 was stirred at room temperature for 6 hours. The solvent was then removed in vacuo and the resulting oil taken up with dichloromethane and washed with aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated. The residue was triturated with diethylether giving 83 mg (60 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.98 - 2.11 (m, 1 H) 2.22 (s, 1 H) 2.77 (t, *J*=7.62 Hz, 2 H) 2.92 - 3.02 (m, 2 H) 3.14 - 3.55 (m, 4 H) 4.31 (s, 3 H) 4.44 - 4.57 (m, 1 H) 7.27 (s, 2 H) 8.29 (s, 1 H) 8.76 (s, 1 H)

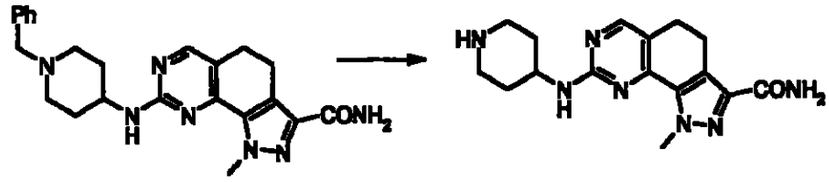
Analogously the following compound was prepared:

N,1-dimethyl-8-(piperidin-4-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B79-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.82 (m, 2 H) 2.05 - 2.16 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.75 - 2.80 (m, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 3.01 - 3.09 (m, 2 H) 3.27 - 3.49 (m, 2 H) 3.93 - 4.10 (m, 1 H) 4.31 (s, 3 H) 7.59 (s, 1 H) 8.07 (q, *J*=4.47 Hz, 1 H) 8.26 (s, 1 H) 8.44 - 8.63 (m, 1 H) 8.69 - 8.90 (m, 1 H).

Example 34

1-methyl-8-(piperidin-4-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B79-X00-M00(C01)-D03]

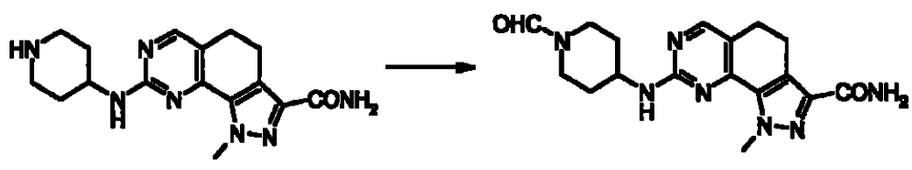


To a solution of 1 g (2.4 mmol) of 8-[(1-benzylpiperidin-4-yl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide in 90 mL of absolute ethanol 1 g of palladium on charcoal 10 % w and 30 mL of 98 % formic acid were added. The resulting mixture was stirred at 60°C for 12 hours. The catalyst was then filtered on celite and the filtrate evaporated. The crude was purified by chromatography on a silica gel column eluted with a mixture CH_2Cl_2-MeOH-Et_3N, giving 350 mg (45 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.77 (m, 2 H) 2.04 - 2.17 (m, 2 H) 2.75 (t, *J*=7.56 Hz, 2 H) 2.96 (t, *J*=7.56 Hz, 2 H) 2.99 - 3.09 (m, 2 H) 3.28 - 3.44 (m, 2 H) 3.93 - 4.08 (m, 1 H) 4.31 (s, 3 H) 7.25 (s, 1 H) 7.31 (d, *J*=7.56 Hz, 1 H) 7.43 (s, 1 H) 8.25 (s, 1 H).

Example 35

8-[(1-formylpiperidin-4-yl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B169-X00-M00(C01)-D03

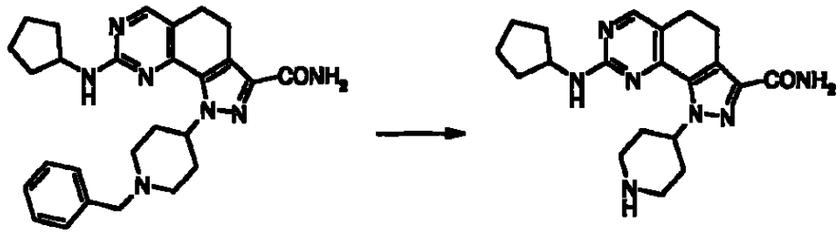


500 mg (1.53 mmol) of 1-methyl-8-(piperidin-4-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide were dissolved in 10 mL of dimethylformamide, containing 253 mg (1.68 mmol) of tert-butyldimethylsilyl chloride, 0.26 mL of triethylamine and 7 mg of 4-dimethylaminopyridine (0.06 mmol), and the mixture stirred at 35-40°C for 25 hours under nitrogen. The mixture was then partitioned between dichloromethane and water, the organic layer was separated, washed with brine and dried over sodium sulfate. Evaporation of the volatiles in vacuo afforded 435 mg (80% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 - 1.48 (m, 2 H) 1.88 - 2.03 (m, 2 H) 2.74 (t, *J*=7.68 Hz, 2 H) 2.77 - 2.87 (m, 1 H) 2.95 (t, *J*=7.62 Hz, 2 H) 3.10 - 3.20 (m, 1 H) 3.66 - 3.79 (m, 1 H) 3.93 - 4.05 (m, 1 H) 4.09 - 4.17 (m, 1 H) 4.31 (s, 3 H) 7.13 (d, *J*=6.83 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.01 (s, 1 H) 8.23 (s, 1 H).

Example 36

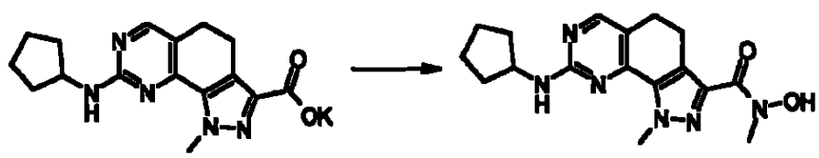
8-(cyclopentylamino)-1-piperidin-4-yl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B73-X00-M00(C18)-D03]



500 mg (1.1 mmol) of 1-(1-benzylpiperidin-4-yl)-8-(cyclopentylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide were dissolved in 50 mL of acetic acid and 50 mg of PtO_2 were added. The mixture was submitted to hydrogenation at 60 psi at room temperature. After 12 hours the catalyst was filtered on celite and the filtrate evaporated. The residue was redissolved with dicholoromethane and washed with aqueous $NaHCO_3$. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure. The title compound (80 % yield) was collected by filtration after trituration with diethylether.

Example 37

8-(cyclopentylamino)-N-hydroxy-N,1-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B73-X00-M00(C01)-D142]



To a suspension of 400 mg (1.14 mmol) of potassium 8-(cyclopentylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in 80 mL of dichloromethane and a few drops of dimethylformamide 0.11 mL (0.13 mmol) of oxalyl chloride were added at 0°C. The mixture was stirred at room temperature for 6 hours and then evaporated, redissolved in anhydrous dichloromethane and dropped into a solution of 344 mg (2.28 mmol) of N-methylhydroxylamine hydrochloride and 0.33 mL of triethylamine in 20 mL of the same solvent, cooled to 0°C. After 4 hours the mixture was washed with a saturated solution of sodium hydrogenocarbonate, dried over sodium sulfate and evaporated to dryness. The residue was triturated with diethylether and filtered to give 780 mg (60 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.61 (m, 4 H) 1.64 - 1.78 (m, 2 H) 1.87 - 2.01 (m, 2 H) 2.67 - 2.89 (m, 4 H) 3.35 (s, 3 H) 4.11 - 4.23 (m, 1 H) 4.31 (s, 3 H) 7.06 (d, *J*=6.58 Hz, 1 H) 8.20 (s, 1 H) 9.88 (s, 1 H).

Analogously, but employing the suitable hydroxylamino derivatives, the following compounds were prepared:

N-cyclohexyl-8-(cyclopentylamino)-N-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B73-X00-M00(C01)-D29]

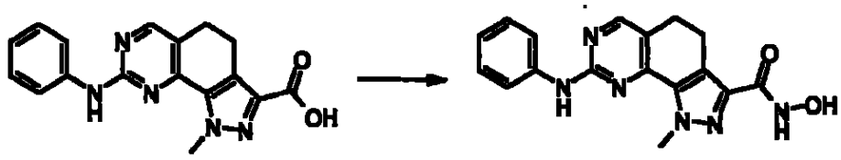
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96 - 2.04 (m, 18 H) 2.67 - 2.81 (m, 4 H) 4.04 - 4.45 (m, 2 H) 4.30 (s, 3 H) 6.97 - 7.10 (m, 1 H) 8.20 (s, 1 H) 9.45 (s, 1 H);

N-benzyl-8-(cyclopentylamino)-N-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B73-X00-M00(C01)-D28]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 - 1.61 (m, 4 H) 1.64 - 1.79 (m, 2 H) 1.87 - 2.00 (m, 2 H) 2.70 - 2.88 (m, 4 H) 4.08 - 4.22 (m, 1 H) 4.31 (s, 3 H) 5.01 (s, 2 H) 7.06 (d, *J*=6.58 Hz, 1 H) 7.22 - 7.43 (m, 5 H) 8.21 (s, 1 H) 9.89 (s, 1 H).

Example 38

8-anilino-N-hydroxy-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B04-X00-M00(C01)-D05]



To a solution of 260 mg (0.81 mmol) of 8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid in 50 mL of anhydrous dimethylformamide 111 mg of N-hydroxybenzotriazole (0.81 mmol), 0.16 mL of N-methylmorpholine, 205 mg (1.07 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride and 585 mg (2.13 mmol) of triphenylmethylhydroxylamine were added consecutively. After 48 hours at room temperature the solvent was removed under reduced pressure and the residue taken up with dichoromethane and washed with water. The organic layer was then dried over sodium sulfate and evaporated. The crude was treated with 10 mL of a mixture dichloromethane-trifluoroacetic acid and after 4 hours the volatiles were removed in vacuo. The residue was redissolved with dichoromethane and washed with aqueous $NaHCO_3$ and the product purified by chromatography on a silica gel column, eluted with CH_2Cl_2-CH_3COCH_3 4/1, to give 180 mg (66 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 - 2.91 (m, 2 H) 2.93 - 3.06 (m, 2 H) 4.33 (s, 3 H) 6.97 (tt, *J*=7.35, 1.07 Hz, 1 H) 7.31 (dd, *J*=8.47, 7.38 Hz, 2 H) 7.72 (dd, *J*=8.66, 1.10 Hz, 2 H) 8.42 (s, 1 H) 8.91 (s, 1 H) 9.52 (s, 1 H) 10.93 (s, 1 H)

Example 39

8-Iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide

[B73-X00-M00(C01)-D03]

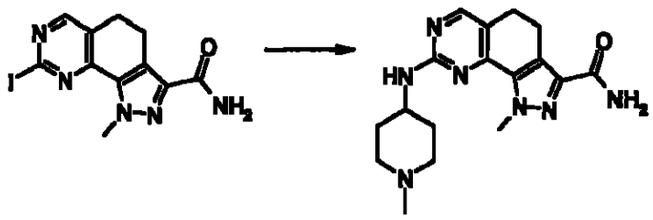


1.0 g (2.6 mmol) of ethyl 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in a mixture of 100 mL of methanol and 100 mL of ammonium hydrate 33%. The solution was stirred in a close bottle at 60°C for 4 hours. The resulting precipitate was collected giving 0.5 g (54% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.99 (m, 4 H) 4.25 (s, 3 H) 7.31 (s, 1 H) 7.51 (s, 1 H) 8.47 (s, 1 H)

Example 40

1-methyl-8-[(1-methylpiperidin-4-yl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B90-X00-M00(C01)-D03]

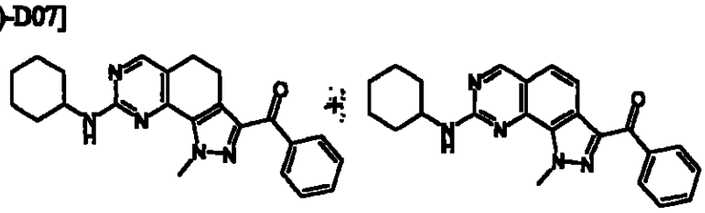


8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (0.10 g, 0.28 mmol) and 1-methylpiperidin-4-amine (0.19 g, 1.7 mmol) were heated at 80°C under nitrogen for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column (eluant: dichloromethane/ethanol/ammonium hydroxide 90/10/1) to give 0.047 mg of 1-methyl-8-[(1-methylpiperidin-4-yl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (50% yield).

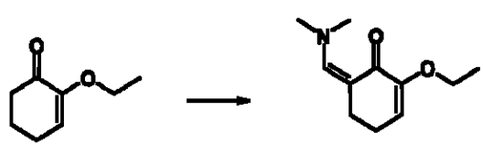
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 2 H) 1.91 (m, 2 H) 2.06 (m, 2 H) 2.4 (s, 3 H) 2.73 (m, 2 H) 2.83 (m, 2 H) 2.94 (m, 2 H) 3.70 (m, 1 H) 4.30 (s, 3 H) 7.01 (m, 1 H) 7.25 (s, 1 H) 7.44 (s, 1 H) 8.29 (s, 1 H)

Example 41

[8-(cyclohexylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B27-X00-M01(C01)-D07] and [8-(cyclohexylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B27-X00-M01(C01)-D07]

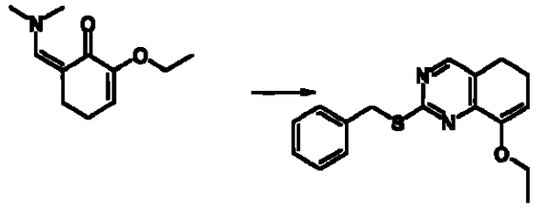


Step 1. 6-[(dimethylamino)methylene]-2-ethoxycyclohex-2-en-1-one



3.4 g (0.02 mmol) of 2-ethoxycyclohex-2-en-1-one were dissolved in 30 mL of dry dimethylformamide and 30 mL (0.05 mmol) of dimethylformamide dimethyl acetale were added. The solution was stirred at 60°C for 2 hours. The solvent was then evaporated under vacuum, the residue triturated with diethyl ether and collected by filtration to give 6.6 g of the title compound (80% yield).

Step 2. 2-(benzylthio)-8-ethoxy-5,6-dihydroquinazoline



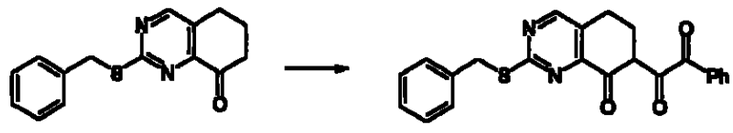
To a solution of 2.0 g (0.01 mol) of 6-[(dimethylamino)methylene]-2-ethoxycyclohex-2-en-1-one in 20 mL of dimethylformamide 2.6 g of S-benzylisothiourea (2 eq.mol.) were added. The reaction mixture was stirred at 95°C for 4 hours. The solvent was then evaporated under reduced pressure and the crude purified by chromatography on a silica gel column (eluant dichloromethane/methanol 9/1) leading 1.5 g (50% yield) of the title compound.

Step 3. 2-(benzylthio)-6,7-dihydroquinazolin-8(5 H)-one



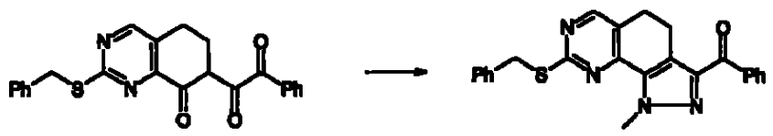
1.5 g (5 mmol) of 2-(benzylthio)-8-ethoxy-5,6-dihydroquinazoline were dissolved in 50 mL of acetic acid and 3 mL of water. The solution was stirred at refluxing temperature for 4 hours. The solvent was then removed under vacuum, the residue partitioned between dichloromethane and a $NaHCO_3$ saturated solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated, giving 1.0 g (74% yield) of the title compound.

Step 4. 1-[2-(benzylthio)-8-oxo-5,6,7,8-tetrahydroquinazolin-7-yl]-2-phenylethane-1,2-dione



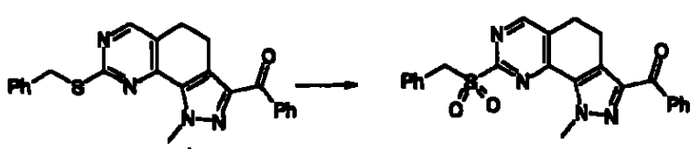
To a solution of 0.22 g (0.81 mmol) of 2-(benzylthio)-6,7-dihydroquinazolin-8(5 H)-one in 5 mL of dry tetrahydrofuran cooled to –50°C, 0.10 g of sodium hydride 60% in mineral oil were added. The resulting suspension was maintained at the same temperature for 30 minutes and then 0.59 mL of ethyl α-oxobenzeneacetate (PhCOCOOEt) were added and the reaction mixture allowed to come to room temperature. After 16 hours the mixture was partitioned between water and ethyl acetate and the organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography on a silica gel column (eluant hexane/ethyl acetate 7/3) giving 0.22 g (68% yield) of the title compound.

Step 5. [8-(benzylthio)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B05-X04-M00(C01)-D07]



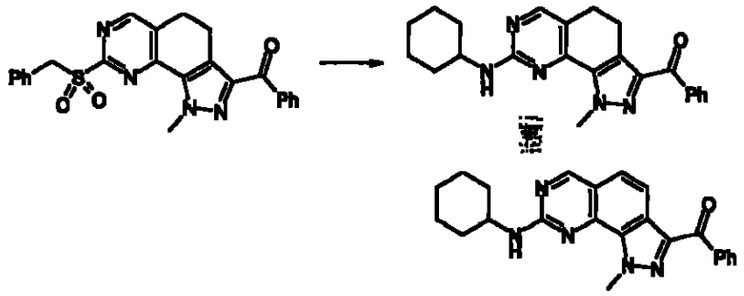
0.22 g (0.55 mmol) of 1-[2-(benzylthio)-8-oxo-5,6,7,8-tetrahydroquinazolin-7-yl]-2-phenylethane-1,2-dione were dissolved in 6 mL of ethanol and 0.03 g (0.66 mmol) of methyl hydrazine were added. The reaction mixture was maintained under stirring at refluxing temperature for 5 hours. After that time the solvent was removed under reduced pressure, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and concentrated, giving 0.16 g of the title compound (70% yield).

Step 6. [8-(benzylsulfonyl)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B05-X05-M00(C01)-D07]



To a solution of 70 mg (0.17 mmol) of [8-(benzylthio)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone in 3 mL of dichloromethane, 115 mg (0.34 mmol) of m-chloroperbenzoic acid were added. The reaction mixture was maintained at room temperature for 1 hour. The solution was then washed with aqueous $NaHCO_3$ and the organic layer was dried over Na_2SO_4 and evaporated in vacuo, giving 70 mg (93% yield) of the title compound.

Step 7. **[8-(cyclohexylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B27-X00-M00(C01)-D07] and [8-(cyclohexylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone [B27-X00-M01(C01)-D07]**



83 mg (0.19 mmol) of [8-(benzylsulfonyl)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone were dissolved in 3 mL of dimethylsulfoxide and cyclohexylamine (0.033mL, 0.29 mmol) and the solution was heated at 100°C under stirring for 16 hours. The solvent was then removed under reduced pressure and the crude purified by chromatography on a silica gel column (eluant dichloromethane/acetone) giving 31 mg of [8-(cyclohexylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone and 15 mg of [8-(cyclohexylamino)-1-methyl-1H-pyrazolo[4,3-h]quinazolin-3-yl](phenyl)methanone (70 % yield overall).

B27-X00-M00(C01)-D07

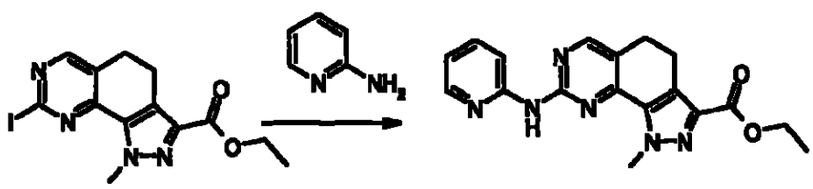
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00-2.00 (5m, 11 H) 2.61 (m, 2 H) 2.66 (m, 2 H) 3.80 (s, 3 H) 7.17 (bs, 1 H) 7.34-7.37 (m, 3 H) 7.41-7.51 (m, 3 H) 8.27 (s, 1 H);

B27-X00-M01(C01)-D07

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20-2.20 (5m, 11 H) 4.02 (bs, 3 H) 6.69 (m, 1 H) 7.37-7.58 (2m, 6 H) 7.93 (bs, 1 H) 8.83 (bs, 1 H).

Example 42

Ethyl 1-methyl-8-(pyridin-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B15-X00-M00(C01)-D01]



Palladium acetate [$Pd(OAc)_2$] (15.3 mg, 0.07 mmol, 10%), (±)-BINAP (42.6 mg, 0.07 mmol, 10%) and dimethylformamide (12 mL) were charged in a round-bottom flask flushed with argon. The mixture was stirred under argon for 30 minutes. Then 2-aminopyridine (70.4 mg, 0.75 mmol), ethyl 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (250 mg, 0.65 mmol), potassium carbonate (1.89 g, 13.67 mmol) and dimethylformamide (5 mL) were added. The resulting mixture was stirred at room temperature for 1 hour and then heated to 120°C in an oil bath under argon with good stirring for 18 hours.

After cooling to room temperature, the reaction mixture was poured into water and extracted with dichloromethane. The organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, the crude solid was taken up with diethyl ether, filtered, washed with diethyl ether and purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 97.5:2.5) to afford 145 mg (63.8% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 3.0 (m, 4 H) 4.3 (q, *J* 7.2 Hz, 2 H) 4.4 (s, 3 H) 7.0 (ddd, *J* 7.2, 4.9, 1.0 Hz, 1 H) 7.8 (ddd, 1 H) 8.2 (d, *J* 8.4 Hz, 1 H) 8.3 (ddd, *J* 4.8, 2.0, 0.9 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H).

By working according to the above method, the following compounds were prepared:

ethyl 8-[(3,5-dichlorophenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B14-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, *J* 7.2 Hz, 2 H) 4.4 (s, 3 H) 7.1 (m, 1 H) 7.4 (m, 2 H) 8.5 (s, 1 H) 10 (s, 1 H);

ethyl 8-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B16-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 3.8 (s, 3 H) 4.3 (q, *J* 7.2 Hz, 2 H) 4.4 (s, 3 H) 6.8 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

ethyl 8-[(4-hydroxyphenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B18-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (m, 5 H) 6.7 (d, *J* 8.8 Hz, 2 H) 7.4 (d, *J* 8.9 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H) 9.2 (s, 1 H);

ethyl 8-(1 H-imidazol-1-ylamino)-1-methyl- 4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B21-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (m, 3 H) 2.9 (m, 4 H) 4.3 (d, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 7.1 (s, 1 H) 7.6 (d, *J* 8.9 Hz, 2 H) 7.7 (s, 1 H) 7.9 (d, *J* 8.9 Hz, 2 H) 8.2 (s, 1 H) 8.5 (s, 1 H) 9.7 (s, 1 H);

ethyl 1-methyl-8-(1,3-thiazol-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B86-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (m, 3 H) 3.0 (m, 4 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 7.1 (d, *J* 3.5 Hz, 1 H) 7.5 (d, *J* 3.7 Hz, 1 H) 8.6 (s, 1 H) 11.6 (s, 1 H);

ethyl 1-methyl-8-(1 H-pyrazol-3-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B77-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 6.5 (s, 1 H) 7.6 (s, 1 H) 8.4 (s, 1 H) 9.6 (s, 1 H) 12.2 (s, 1 H);

ethyl 1-methyl-8-[(4-morpholin-4-ylphenyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B19-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 3.1 (m, 4 H) 3.8 (m, 4 H) 4.3 (q, *J* 7.2 Hz, 2 H) 4.3 (s, 3 H) 6.9 (d, *J* 9.0 Hz, 2 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

ethyl 8-{[4-(ethoxycarbonyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B87-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 6 H) 3.0 (m, 4 H) 4.3 (m, 4 H) 4.4 (s, 3 H) 7.9 (m, 4 H) 8.5 (s, 1 H) 10.0 (s, 1 H);

ethyl 8-{[4-(N,N-diethylamino)phenyl]amino}-}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B17-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (t, *J* 7.0 Hz, 6 H) 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 3.3 (m, 4 H) 4.3 (q, *J* 7.1, 7.1 Hz, 2 H) 4.3 (s, 3 H) 6.7 (d, *J* 9.1 Hz, 2 H) 7.4 (d, *J* 9.0 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H);

ethyl 8-{[4-(acetylamino)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B22-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.0 (s, 3 H) 2.9 (m, 4 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 7.5 (d, *J* 9.0 Hz, 2 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.4 (s, 1 H) 9.8 (s, 1 H);

ethyl 8-{[3-(hydroxymethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B11-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 4.5 (s, 2 H) 6.9 (m, 1 H) 7.3 (t, *J* 7.8 Hz, 1 H) 7.5 (m, 1 H) 7.8 (s, 1 H) 8.4 (s, 1 H) 9.5 (s, 1 H);

ethyl 8-[(4-methoxyphenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B68-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 3.7 (s, 3 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.3 (s, 3 H) 6.9 (d, *J* 9.0 Hz, 2 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

ethyl 8-{[(4-bromo-3-chloro)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B88-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, *J* 7.1 Hz, 2 H) 4.4 (s, 3 H) 7.6 (dd, *J* 8.8, 2.4 Hz, 1 H) 7.7 (d, *J* 8.8 Hz, 1 H) 8.2 (d, *J* 2.4 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

ethyl 8-{[3-bromo-5-(trifluoromethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B115-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.1 Hz, 3 H) 2.95 (m, 4 H) 4.31 (q, *J*=7.2 Hz, 2 H) 4.39 (s, 3 H) 7.49 (s, 1 H) 8.10 (s, 1 H) 8.36 (s, 1 H) 8.54 (s, 1 H) 10.11 (s, 1 H);

ethyl 8-[4-(4-methyl-piperazin-1-yl)-3-(hydroxymethyl)phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B116-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 2.28 (s, 3 H) 2.42 - 2.61 (m, 4 H) 2.79 - 2.88 (m, 6 H) 2.98 (t, *J*=7.80 Hz, 2 H) 4.31 (q, *J*=7.15 Hz, 2 H) 4.36 (s, 3 H) 4.56 (d, *J*=5.24 Hz, 2 H) 5.06 (t, *J*=5.30 Hz, 1 H) 7.03 (d, *J*=8.66 Hz, 1 H) 7.50 (dd, 1 H) 7.81 (d, *J*=2.68 Hz, 1 H) 8.39 (s, 1 H) 9.42 (s, 1 H);

ethyl 1-methyl-8-{[4-(morpholin-4-ylmethyl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B102 -X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.13 Hz, 3 H) 2.35 (s, 4 H) 2.86 (t, *J*=7.62 Hz, 2 H) 2.99 (t, *J*=7.80 Hz, 2 H) 3.42 (s, 2 H) 3.55 - 3.61 (m, 4 H) 4.31 (q, *J*=7.07 Hz, 2 H) 4.37 (s, 3 H) 7.24 (d, *J*=8.41 Hz, 2 H) 7.66 (d, *J*=8.41 Hz, 2 H) 8.42 (s, 1 H) 9.52 (s, 1 H);

ethyl 1-methyl-8-({4-[(1-methylpiperidin-4-yl)oxy]phenyl}amino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B103-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.09 (m, 4 H) 2.86 (m, 5 H) 2.98 (t, 2 H) 3.37 (m, 5 H) 4.30 (q, 2 H) 4.34 (s, 3 H) 7.03 (m, 2 H) 7.61 (m, 2 H) 8.39 (s, 1 H) 9.40 (s, 1 H);

ethyl 1-methyl-8-({3-[(4-methylpiperazin-1-yl)methyl]phenyl}amino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B104-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.21 (m, 3 H) 2.40 (m, 8 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 3.44 (s, 2 H) 4.30 (q, 2 H) 4.39 (s, 3 H) 6.91 (m, 1 H) 7.24 (m, 1 H) 7.56 (m, 1 H) 7.75 (dd, 1 H) 8.43 (m, 1 H) 9.54 (s, 1 H);

ethyl 8-{[3-fluoro-4-(4-methylpiperazin-1-yl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B109-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.28 (s, 3 H) 2.85 (t, 2 H) 2.99 (m, 6 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 7.01 (t, 1 H) 7.35 (dd, 1 H) 7.64 (dd, 1 H) 8.42 (m, 1 H) 9.56 (s, 1 H);

ethyl 8-[(4-chlorophenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B112-X00-M00(C01)-D01]

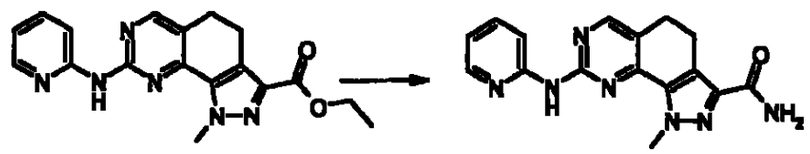
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 7.38 (d, 2 H) 7.74 (d, 2 H) 8.45 (s, 1 H) 9.70 (s, 1 H);

ethyl 8-{[4-(hydroxymethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B114-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 4.45 (s, 2 H) 7.27 (d, 2 H) 7.65 (d, 2 H) 8.42 (s, 1 H) 9.50 (s, 1 H).

Example 43

1-Methyl-8-(pyridin-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B15-X00-M00(C01)-D03]



To a solution of ethyl 1-methyl-8-(pyridin-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (220 mg, 0.63 mmol) in methanol (250 mL), 33% aqueous ammonium hydroxide (100 mL) was added and the solution was stirred at 65°C for 8 hours.

By concentrating the solution, the final compound that precipitated was collected by suction filtration, washed with water and crystallized twice from methanol containing sodium hydroxide, and dried at 40°C under vacuum. There were thus obtained 60 mg of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.0 (m, 4 H) 4.4 (s, 3 H) 7.0 (ddd, *J* 7.2, 4.9, 1.0 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H)7.8 (ddd, 1 H) 8.2 (d, *J* 8.4 Hz, 1 H) 8.3 (ddd, *J* 4.8, 2.0, 0.9 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H)

By working according to the same procedure, the following compounds were prepared:

8-[(3,5-dichlorophenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B14-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (t, *J* 1.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.9 (d, *J* 1.8 Hz, 2 H) 8.5 (s, 1 H) 10.0 (s, 1 H);

8-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B16-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.8 (s, 3 H) 4.3 (s, 3 H) 6.8 (s, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-[(4-hydroxyphenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B18-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 6.7 (d, *J* 8.8 Hz, 2 H) 7.2 (s, 1 H) 7.4 (d, *J* 8.9 Hz, 2 H) 7.5 (s, 1 H) 8.3 (s, 1 H) 9.1 (s, 1 H) 9.2 (s, 1 H);

8-{[4-(1 H-imidazol-1-yl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B21-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.4 (s, 3 H) 7.1 (s, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, *J* 8.9 Hz, 2 H) 7.7 (t, *J* 1.2 Hz, 1 H) 7.9 (d, *J* 9.0 Hz, 2 H) 8.2 (s, 1 H) 8.4 (s, 1 H) 9.7 (s, 1 H);

1-methyl-8-(thiazol-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B86-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (d, *J* 3.7 Hz, 1 H) 7.3 (s, 1 H) 7.5 (d, *J* 3.7 Hz, 1 H) 7.5 (s, 1 H) 8.6 (s, 1 H) 11.8 (s, 1 H);

1-methyl-8-(1 H-pyrazol-3-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B77-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 6.5 (bs, 1 H) 7.25 (s, 1 H) 7.45 (s, 1 H) 7.6 (bs, 1 H) 8.4 (s, 1 H) 9.9 (s, 1 H);

8-{[4-(N-morpholino)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B19-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.1 (m, 4 H) 3.8 (m, 4 H) 4.3 (s, 3 H) 6.9 (d, *J* 9.1 Hz, 2 H) 7.2 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-{[4-(diethylamino)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B17-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (t, *J* 7.0 Hz, 6 H) 2.9 (m, 4 H) 3.3 (m, 4 H) 4.3 (s, 3 H) 6.7 (d, *J* 9.0 Hz, 2 H) 7.2 (s, 1 H) 7.4 (m, *J* 9.0 Hz, 1 H) 7.4 (d, *J* 9.0 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H);

8-{[4-(acetylamino)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B22-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.9 (m, 4 H) 4.3 (s, 3 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (d, *J* 8.9 Hz, 2 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.4 (s, 1 H) 9.8 (s, 1 H);

8-{[3-(hydroxymethyl)phenyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B11-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 4.5 (s, 2 H) 5.2 (s, 1 H) 6.9 (d, *J* 8.0 Hz, 1 H) 7.2 (m, 2 H) 7.5 (s, 1 H) 7.5 (dd, *J* 8.1, 1.4 Hz, 1 H) 7.8 (t, *J* 1.8 Hz, 1 H) 8.4 (s, 1 H) 9.5 (s, 1 H);

8-[(4-methoxyphenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B68-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.7 (s, 3 H) 4.3 (s, 3 H) 6.9 (d, *J* 9.1 Hz, 2 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, *J* 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-[[(4-Bromo-3-chloro)phenyl]amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B88-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.4 (s, 3 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, *J* 8.8, 2.4 Hz, 1 H) 7.7 (d, *J* 8.8 Hz, 1 H) 8.2 (d, *J* 2.4 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-[4-(4-methyl-piperazin-1-yl)-3-(hydroxymethyl)phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B116-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.29 (s, 3 H) 2.45 - 2.61 (m, 4 H) 2.73 - 2.87 (m, 6 H) 2.99 (t, *J*=7.56 Hz, 2 H) 4.34 (s, 3 H) 4.56 (d, *J*=5.24 Hz, 2 H) 5.06 (t, *J*=5.37 Hz, 1 H) 7.03 (d, *J*=8.66 Hz, 1 H) 7.26 (s, 1 H) 7.46 (s, 1 H) 7.50 (dd, *J*=8.23, 2.99 Hz, 1 H) 7.83 (d, *J*=2.68 Hz, 1 H) 8.38 (s, 1 H) 9.40 (s, 1 H);

8-[4-(4-methyl-piperazin-1-yl)-3-(hydroxymethyl)phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B116-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.45 - 2.55 (m, 4 H) 2.75 (d, *J*=4.63 Hz, 3 H) 2.81 (t, *J*=7.19 Hz, 2 H) 2.83 (t, *J*=4.63 Hz, 4 H) 2.99 (t, *J*=7.56 Hz, 2 H) 4.34 (s, 3 H) 4.56 (d, *J*=5.24 Hz, 2 H) 5.05 (t, *J*=5.37 Hz, 1 H) 7.03 (d, *J*=8.54 Hz, 1 H) 7.50 (d, *J*=8.41, 2.56 Hz, 1 H) 7.83 (d, *J*=2.68 Hz, 1 H) 8.07 (q, *J*=4.63 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H);

8-[4-(4-methyl-piperazin-1-yl)-3-(bromo)phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide trihydrochloride [B117-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 2.88 (d, *J*=4.68 Hz, 3 H) 3.01 (m, 4 H) 3.19 (m, 2 H) 3.53 (m, 2 H) 4.37 (s, 3 H) 7.23 (m, 1 H) 7.29 (s, 1 H) 7.46 (s, 1 H) 7.63 (m, 1 H) 8.21 (m, 1 H) 8.44 (s, 1 H) 9.67 (s, 1 H) 10.13 (s, 1 H);

8-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B104-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.44 (s, 4 H) 2.78 - 3.03 (m, 4 H) 3.04 - 3.40 (m, 4 H) 3.45 (s, 2 H) 4.37 (s, 3 H) 6.90 (d, *J*=7.32 Hz, 1 H) 7.25 (t, *J*=7.68 Hz, 1 H) 7.27 (s, 1 H) 7.46 (s, 1 H) 7.57 (dd, *J*=7.68, 1.59 Hz, 1 H) 7.76 (t, *J*=1.77 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H);

8-{[(3-hydroxy)-5-trifluoromethyl]phenylamine}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B118-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.77 - 3.07 (m, 4 H) 3.84 (s, 3 H) 4.35 (s, 3 H) 6.84 (s, 1 H) 7.28 (s, 1 H) 7.47 (s, 1 H) 7.57 (s, 1 H) 7.85 (s, 1 H) 8.49 (s, 1 H) 9.86 (s, 1 H);

8-[4-(4-methyl-piperazin-1-yl)-phenylamine]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B10-X00-M00(C01)-D04]

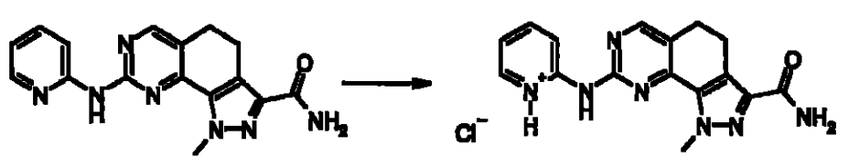
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (d, *J*=4.76 Hz, 3 H) 2.81 (t, *J*=7.68 Hz, 2 H) 2.85 (d, *J*=4.39 Hz, 3 H) 2.94 - 3.07 (m, 4 H) 3.11 - 3.25 (m, 2 H) 3.51 (d, *J*=11.83 Hz, 2 H) 3.73 (d, *J*=13.66 Hz, 2 H) 4.33 (s, 3 H) 6.99 (d, *J*=9.15 Hz, 2 H) 7.60 (d, *J*=9.02 Hz, 2 H) 8.08 (q, *J*=4.67 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H) 10.36 (s, 1 H);

8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B04-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, *J*=4.76 Hz, 3 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, *J*=7.38 Hz, 1 H) 7.21 - 7.32 (m, 2 H) 7.68 (d, *J*=7.56 Hz, 2 H) 8.06 (q, *J*=4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H).

Example 44

1-Methyl-8-(pyridin-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide hydrochloride



To a solution of 1-methyl-8-(pyridin-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide in a 1:1 mixture of methanol and dichloromethane, 4 N HCl in dioxane (1 mL) was added. After 1 hour at room temperature the solvent was removed under vacuum and the solid was triturated with diethyl ether affording the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.3 (m, 2 H) 7.5 (s, 1 H) 7.8 (d, *J* 8.8 Hz, 1 H) 8.2 (t, *J* 7.7 Hz, 1 H) 8.4 (dd, *J* 5.9, 1.0 Hz, 2 H) 8.6 (s, 1 H) 11.6 (s, 1 H).

By working according to this method, the following compounds were prepared:

1-methyl-8-(thiazol-2-ylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide hydrochloride

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (d, *J* 3.7 Hz, 1 H) 7.3 (s, 1 H) 7.5 (d, *J* 3.7 Hz, 1 H) 7.5 (s, 1 H) 8.6 (s, 1 H) 11.8 (s, 1 H);

8-[4(N-Methylpiperazino)-3-chlorophenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide trichlorohydrate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.1 (m, 15 H) 4.4 (s, 3 H) 7.2 (d, *J* 8.9 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, *J* 8.8, 2.4 Hz, 1 H) 8.0 (d, *J* 2.6 Hz, 1 H) 8.4 (s, 1 H) 9.7 (s, 1 H) 10.5 (s, 1 H);

8-[4(N-Methylpiperazino)-3-bromophenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide trichlorohydrate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.1 (m, 15 H) 4.4 (s, 3 H) 7.2 (d, *J* 8.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, *J* 8.6, 2.4 Hz, 1 H) 8.0 (d, *J* 2.6 Hz, 1 H) 8.2 (s, 1 H) 9.7 (s, 1 H) 10.5 (s, 1 H);

N-benzyl-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (L)-tartrate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H) 2.70 (m, 4 H) 2.80 (t, *J*=7.62 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.14 (m, 4 H) 4.20 (s, 2 H) 4.34 (s, 3 H) 4.43 (d, *J*=6.34 Hz, 2 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.27 (m, 5 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 8.69 (t, *J*=6.34 Hz, 1 H) 9.28 (s, 1 H);

1-methyl-8-[(4-morpholin-4-ylphenyl)amino]-N-[(1R)-1-phenylethyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide hydrochloride

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.97 (m, 4 H) 3.21 (m, 4 H) 3.84 (m, 4 H) 4.37 (m, 3 H) 5.15 (m, 1 H) 7.28 (m, 7 H) 7.63 (m, 2 H) 8.40 (m, 1 H) 8.44 (m, 1 H) 9.50 (m, 1 H);

N-(3-fluorobenzyl)-1-methyl-8-[(4-morpholin-4-ylphenyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide hydrochloride

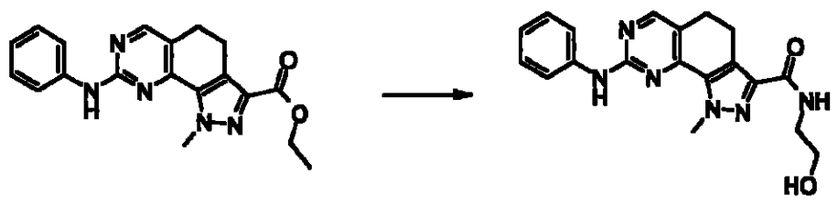
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (m, *J*=73.53 Hz, 4 H) 3.16 (m, 4 H) 3.81 (m, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 7.07 (m, 6 H) 7.61 (m, 2 H) 8.37 (m, 1 H) 8.80 (m, 1 H) 9.44 (m, 1 H);

N-(3-fluorobenzyl)-1-methyl-8-[(4-morpholin-4-ylphenyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide methanesulfonate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.00 (s, 4 H) 3.17 (s, 4 H) 3.80 (s, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 7.07 (m, 6 H) 7.61 (m, 2 H) 8.37 (m, 1 H) 8.80 (m, 1 H) 9.46 (m, 1 H).

Example 45

8-anilino-N-(2-hydroxyethyl)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B04-X00-M00(C01)-D06]



To a suspension of 0.30 g (0.86 mmol) of ethyl 8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate in a mixture of 10 mL of methanol and 10 mL of dimethylformamide, 5 mL of ethanolamine were added. The mixture was heated in a close bottle under stirring at 65 °C. After 5 hours the solvent was removed, the residue redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The residue was triturated with diethyl ether and the product collected by filtration (60 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.7-3.0 (2m, 4 H) 3.47 (m, 4 H) 4.32 (s, 3 H) 4.71 (t, 1 H) 6.94-7.67 (3m, 5 H) 7.91 (t, *J* 5.73 Hz, 1 H) 8.38 (bs, 1 H) 9.48 (bs, 1 H).

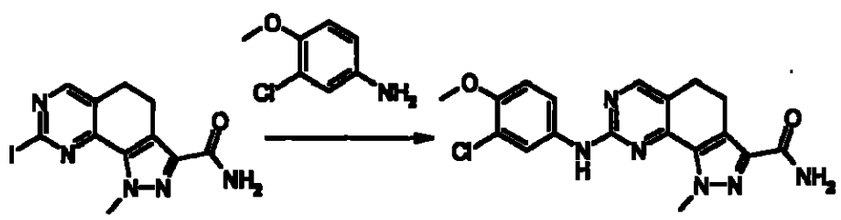
By working analogously the following compound was prepared:

8-anilino-N,1-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B04-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, *J* 4.76 Hz, 3 H) 2.79 (t, *J* 7.68 Hz, 2 H) 2.97 (t, *J* 7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, *J* 7.38 Hz, 1 H) 7.28 (m, 2 H) 7.68 (d, *J* 7.56 Hz, 2 H) 8.06 (q, *J* 4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H).

Example 46

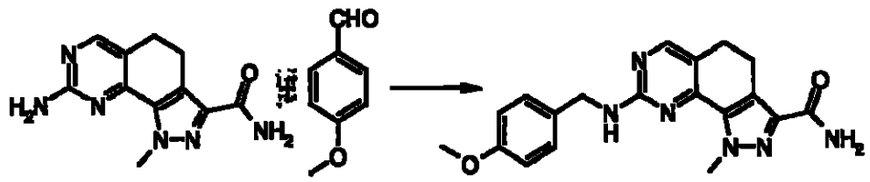
8-[(4-methoxy-3-chlorophenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B20-X00-M00(C01)-D03]



$Pd(OAc)_2$ (20 mg, 0.09 mmol, 10%), (±)-BINAP (55 mg, 0.09 mmol, 10%) and dimethylformamide (15 mL) were charged in a round-bottom flask flushed with argon. The mixture was stirred under argon for 30 minutes. Then 3-chloro-*p*-anisidine (153 mg, 0.97 mmol), 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (300 mg, 0.84 mmol), K_2CO_3 (2.45 g, 17.8 mmol) and dimethylformamide (6 mL) were added. The resulting mixture was stirred at room temperature for 1 hour and then heated to 120°C in an oil bath under argon with good stirring for 18 hours.
After cooling to room temperature, the reaction mixture was poured into water (300 mL) and extracted with dichloromethane (5 x 60 mL). The organic extracts were washed with water (2 x 20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum, the crude solid was taken up with diethyl ether, filtered, washed with diethyl ether and purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 97.5:2.5) to afford 95 mg of pure title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.8 (s, 3 H) 4.3 (s, 3 H) 7.1 (d, *J* 9.0 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (dd, *J* 9.0, 2.6 Hz, 1 H) 7.9 (d, *J* 2.6 Hz, 1 H) 8.4 (s, 1 H) 9.5 (s, 1 H)
By working according to the same procedure the following compound was prepared:
8-[4(N-Methyl-N-piperazinyl)-3-chlorophenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B13-X00-M00(C01)-D03]
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.3 (s, 3 H) 2.5 (m, 4 H) 2.9 (m, 8 H) 4.4 (s, 3 H) 7.1 (d, *J* 8.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (dd, *J* 8.8, 2.4 Hz, 1 H) 8.0 (d, *J* 2.6 Hz, 1 H) 8.4 (s, 1 H) 9.6 (s, 1 H).

Example 47

8-[(4-methoxybenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B60-X00-M00(C01)-D03]



To a solution of 8-amino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (244 mg, 1.0 mmol) in a mixture of glacial acetic acid/methanol/water (1:1:1) (30 mL) in a round-bottom flask were added p-methoxybenzaldehyde (0.44 mL, 450 mg, 3.0 mmol) and then 85% sodium cyanoborohydride (210 mg, 2.0 mmol). The solution was stirred at room temperature for 7 hours. At that time further amount of aldehyde (0.44 mL) and sodium cyanoborohydride (210 mg) were added and stirring was continued overnight.

The reaction mixture was poured into ice-water (200 mL), the pH was adjusted to 10 by addition of saturated sodium carbonate and the solution extracted with ethyl acetate (4 x 20 mL). The collected organic extracts were washed with brine until neutral, with water and dried over Na_2SO_4.

Evaporation of the solvent under vacuum left a yellow solid residue that was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 95:5) to yield 250 mg of yellow pure compound. Crystallization from methanol afforded 225 mg of crystalline title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 3.7 (s, 3 H) 4.2 (s, 3 H) 4.5 (d, *J* 6.1 Hz, 2 H) 7.2 (s, 1 H) 6.8 (d, *J* 8.8 Hz, 2 H) 7.4 (s, 1 H) 7.3 (d, *J* 8.8 Hz, 2 H) 7.6 (m, 1 H) 8.2 (s, 1 H)

By working according to this method, the following compounds were prepared:

1-methyl-8-[(thien-3-ylmethyl)amino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B43-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (d, *J* 6.1 Hz, 2 H) 7.1 (m, 1 H) 7.2 (s, 1 H) 7.3 (m, 1 H) 7.4 (s, 1 H) 7.5 (m, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H);

8-[(3,5-dihydroxybenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B62-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (m, 2 H) 4.3 (s, 3 H) 4.4 (d, *J* 6.2 Hz, 2 H) 6.0 (m, 1 H) 6.2 (m, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H);

8-({4-[3-(dimethylamino)propoxy]benzyl}amino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B61-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.8 (m, 2 H) 2.2 (s, 6 H) 2.4 (t, 2 H) 2.8 (m, 4 H) 4.0 (t, 2 H) 4.3 (s, 3 H) 4.5 (d, *J* 6.5 Hz, 2 H) 6.9 (m, *J* 9.0 Hz, 2 H) 7.2 (d, *J* 8.7 Hz, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H);

[5-({[3-(aminocarbonyl)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazolin-8-yl]amino}methyl)-2-furyl]methyl acetate [B65-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.8 (m, 4 H) 4.3 (s, 3 H) 4.5 (d, *J* 6.1 Hz, 2 H) 5.0 (s, 2 H) 6.2 (d, *J* 3.2 Hz, 1 H) 6.4 (d, *J* 3.2 Hz, 1 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (t, *J* 6.0 Hz, 1 H) 8.2 (s, 1 H);

8-[(3-cyanobenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B63-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.1 (s, 3 H) 4.6 (d, *J* 6.1 Hz, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.5 (t, *J* 7.7 Hz, 1 H) 7.7 (m, 4 H) 8.2 (s, 1 H);

8-[(4-Bromobenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B64-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (d, *J* 6.3 Hz, 2 H) 7.2 (s, 1 H) 7.3 (d, *J* 8.5 Hz, 2 H) 7.4 (s, 1 H) 7.5 (d, *J* 8.5 Hz, 2 H) 7.7 (m, 1 H) 8.2 (s, 1 H);

8-{[4-(acetylamino)benzyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B80-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.7 (m, 2 H) 2.9 (t, *J* 7.7 Hz, 2 H) 4.2 (s, 3 H) 4.5 (d, *J* 6.2 Hz, 2 H) 7.2 (s, 1 H) 7.3 (d, *J* 8.5 Hz, 2 H) 7.4 (s, 1 H) 7.5 (d, *J* 8.5 Hz, 2 H) 7.6 (t, *J* 7.4 Hz, 1 H) 8.2 (s, 1 H) 9.9 (s, 1 H);

B81-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.7 (m, 2 H) 2.9 (t, *J* 7.6 Hz, 2 H) 4.3 (s, 3 H) 4.3 (s, 2 H) 4.5 (d, *J* 6.0 Hz, 2 H) 5.1 (s, 1 H) 6.2 (m, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (t, *J* 5.9 Hz, 1 H) 8.2 (s, 1 H);

8-[(1-Methylimidazol-2-yl)methylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B82-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 3.7 (s, 3 H) 4.3 (s, 3 H) 4.6 (m, 2 H) 6.9 (s, 1 H) 7.17 (s, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.5 (m, 1 H) 8.3 (s, 1 H);

8-[(4-Aminobenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B83-X00-M00(C01)-D03]

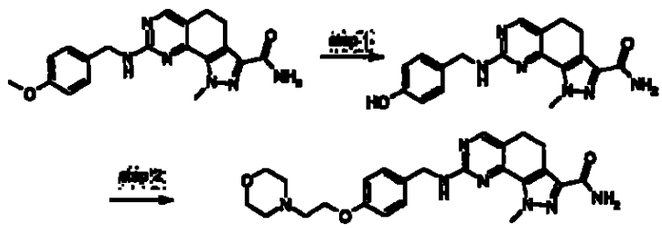
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.7 (m, 2 H) 2.9 (t, *J* 7.7 Hz, 2 H) 4.3 (s, 3 H) 4.4 (d, *J* 6.1 Hz, 2 H) 5.1 (s, 2 H) 6.5 (d, *J* 8.4 Hz, 2 H) 7.0 (d, *J* 8.3 Hz, 2 H) 7.2 (s, 1 H) 7.4 (m, 2 H) 8.2 (s, 1 H);

8-[(4-Fluorobenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, *J*=7.74 Hz, 2 H) 2.94 (t, *J*=7.56 Hz, 2 H) 4.18 (s, 3 H) 4.52 (d, *J*=6.22 Hz, 2 H) 7.13 (t, *J*=8.90 Hz, 2 H) 7.23 (s, 1 H) 7.38 (dd, *J*=8.66, 5.61 Hz, 2 H) 7.42 (t, 1 H) 7.71 (t, *J*=5.97 Hz, 1 H) 8.23 (s, 1 H).

Example 48

8-{[4-(2-morpholinoethoxy)benzyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B84-X00-M00(C01)-D03]



Step 1. 8-[(4-Hydroxybenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B85-X00-M00(C01)-D03]

To a well stirred solution of 8-[(4-methoxybenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (242 mg, 0.7 mmol) in chloroform (30 mL) boron tribromide (1 M in dichloromethane, 5.12 mL, 5.1 mmol) was added dropwise over a 5 minutes period, at room temperature. The mixture was heated to reflux for 8 hours. A solution of 10% aqueous ammonium hydroxide (30 mL) was added dropwise at 0°C over a 10 minutes period. A precipitate was formed and, after 2 hours, it was filtered and washed with water and dried at 40°C under vacuum. There were obtained 130 mg of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (m, 2 H) 6.7 (d, *J* 8.65 Hz, 2 H) 7.2 (d, *J* 8.5 Hz, 2 H) 7.25 (s, 1 H) 7.4 (s, 1 H) 7.8 (m, 1 H) 8.2 (s, 1 H)

Step 2. 8-{[4-(2-morpholinoethoxy)benzyl]amino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B84-X00-M00(C01)-D03]

To a solution of 8-[(4-hydroxybenzyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (70 mg, 0.2 mmol) in anhydrous dimethylformamide (3 mL), N-morpholinoethylchloride hydrochloride (47 mg, 0.3 mmol) and powdered potassium carbonate (45 mg, 3.3 mmol) were added. The mixture was heated to reflux for 1 hour. The reaction mixture was poured into iced water (70 mL) and extracted with dichloromethane; the organic extracts were washed with brine until neutral pH, then with water and dried over Na_2SO_4. The crude was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 96:4) to yield a white solid that was crystallized from methanol, affording 47.0 mg of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.5 (m, 4 H) 2.7 (t, 2 H) 2.8 (m, 4 H) 3.6 (m, 4 H) 4.0 (t, 2 H) 4.2 (s, 3 H) 4.5 (m, 2 H) 6.9 (d, *J* 8.42 Hz, 2 H) 7.2 (s, 1 H) 7.25 (d, *J* 8.54 Hz, 2 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H).

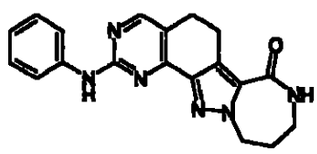
Analogously the following compound was prepared:

8-{[3-(2-morpholinoethoxy)-5-trifluoromethyl]phenylamino}-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B119-X00-M00(C01)-D03]

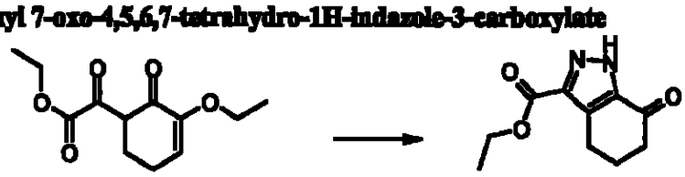
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.47 - 2.56 (m, 4 H) 2.73 (t, *J*=7.26 Hz, 2 H) 2.85 (t, *J*=7.80 Hz, 2 H) 3.01 (t, *J*=7.80 Hz, 2 H) 3.57 - 3.64 (m, 4 H) 4.17 (t, *J*=5.49 Hz, 2 H) 4.35 (s, 3 H) 6.86 (t, *J*=1.83 Hz, 1 H) 7.28 (s, 1 H) 7.48 (s, 1 H) 7.61 (t, *J*=2.32 Hz, 1 H) 7.80 (t, *J*=1.46 Hz, 1 H) 8.49 (s, 1 H) 9.85 (s, 1 H).

Example 49

2-anilino-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B04-X00-M06]



Step 1. Ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



1 g (4.2 mmol) of ethyl (3-ethoxy-2-oxocyclohex-3-en-1-yl)(oxo)acetate were dissolved in 10 mL of ethanol, 0.21 mL of hydrazine hydrate were added and the solution stirred at reflux for a day. The solvent was then evaporated and the residue redissolved with

dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The crude was triturated with diethyl ether and filtered to give (70 % yield) the title compound.

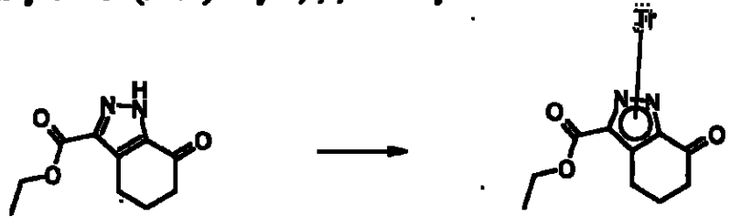
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J* 6.83 Hz 3 H) 2.25-3-27 (3m, 6 H) 4.18 (q, *J* 6.83 Hz, 2 H) 8.45 (bs, 1 H).

Analogously the following compound was prepared:

Ethyl 4,4-dimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=6.95 Hz, 3 H) 1.42 (s, 6 H) 1.90 - 2.02 (m, 2 H) 2.55 - 2.63 (m, 2 H) 4.33 (q, *J*=6.95 Hz, 2 H) 14.34 (s, 1 H).

Step 2, **Ethyl 7-oxo-1(and 2)-trityl-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate**



1.20 g (4.8 mmol) of ethyl 7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 40 mL of dichloromethane and 0.76 mL of triethylamine and 1.47 g (5.3 mmol) of triphenylmethyl chloride were added. The solution was stirred at room temperature for 6 hours. Then the solution was diluted with further dichloromethane and washed with water. The organic layer was treated with anhydrous Na_2SO_4 and evaporated to dryness. The product, as a mixture of regioisomers, was finally obtained by crystallization from diethyl ether (80 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, 3 H) 1.94-2.98 (3m, 6 H) 4.25 (q, 2 H) 6.85-7.36 (2m, 15 H).

Analogously the following compounds were prepared:

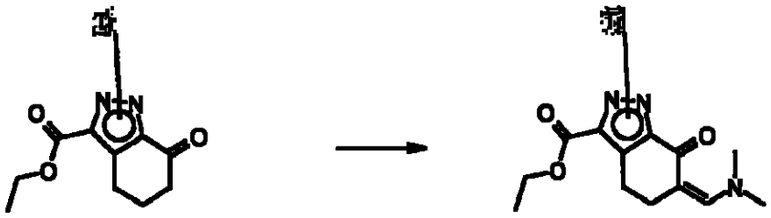
Ethyl 1-trityl-4,4-dimethyl-7-oxo-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.26 (t, *J*=7.07 Hz, 3 H) 1.45 (s, 6 H) 1.79 - 1.88 (m, 2 H) 2.18 - 2.26 (m, 2 H) 4.27 (q, *J*=7.15 Hz, 2 H) 6.84 - 7.01 (m, 6 H) 7.14 - 7.33 (m, 9 H);

Ethyl 2-trityl-4,4-dimethyl-7-oxo-4,5,6,7-tetrahydro-1 H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (t, *J*=7.13 Hz, 3 H) 1.27 (s, 6 H) 1.92 - 1.99 (m, 2 H) 2.56 - 2.63 (m, 2 H) 3.44 (q, *J*=7.15 Hz, 2 H) 6.99 - 7.05 (m, 6 H) 7.31 - 7.37 (m, 9 H).

Step 3. Ethyl -6-[(dimethylamino)methylene]-7-oxo-1(2)-trityl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate



3.0 g (6.6 mmol) of ethyl 7-oxo-1(2)-trityl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate were dissolved in 20 mL of dimethylformamide and 3.2 mL (13.2 mmol) of dimethylformamide ditertbutylacetale were added. The solution was heated at 65°C under stirring for a day and then evaporated to dryness. The product was obtained by crystallization from a mixture diethyl ether/ethyl acetate (90 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 and 0.79 (2t, *J* 7.07 Hz, 3 H) 2.70-2.90 (2t, *J* 6.71 Hz, 6 H) 2.94 and 2.99 (2m, 6 H) 4.21 (q, *J* 7.07 Hz, 2 H) 6.90-7.30 (m, 15 H).

Analogously the following compounds were prepared:

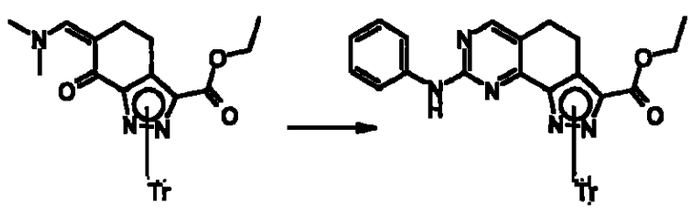
Ethyl 6-[(dimethylamino)methylene]-1-trityl-4,4-dimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, *J*=7.13 Hz, 3 H) 1.36 (s, 6 H) 2.66 (s, 2 H) 2.98 (s, 6 H) 4.25 (q, *J*=7.15 Hz, 2 H) 6.96 (t, 7 H) 7.15 - 7.29 (m, 9 H);

Ethyl 6-[(dimethylamino)methylene]-2-trityl-4,4-dimethyl-7-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (t, *J*=7.19 Hz, 3 H) 1.19 (s, 6 H) 2.78 (s, 2 H) 3.11 (s, 6 H) 3.42 (q, *J*=7.23 Hz, 2 H) 6.97 - 7.09 (m, 6 H) 7.30 - 7.37 (m, 9 H) 7.48 (s, 1 H).

Step 4. Ethyl 8-anilino-1(and 2)-trityl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate



To a solution of 636 mg of ethyl 6-[(dimethylamino)methylene]-7-oxo-1(2)-trityl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (1.18 mmol) and 440 mg (1.18 mmol) of

phenylguanidine carbonate in 100 mL of absolute ethanol, 0.5 mL of diazabicycloundecene were added. The mixture was stirred at reflux for 48 hours and then the solvent evaporated under reduced pressure. The residue was redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and purified by chromatography on a silica gel column (eluant cyclohexane/ethyl acetate 8/2) to give 240 mg of the title compound (35% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 (t, *J* 7.20 Hz, 3 H) 2.80-2.95 (m, 4 H) 3.58 (q, *J* 7.20 Hz, 2 H) 6.85-7.80 (5m, 20H) 8.38 (bs, 1 H) 9.49 (bs, 1 H).

According to the same method but employing the suitable guanidine derivatives, the following compounds were prepared:

Ethyl 8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-1(and 2)-trityl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-1(and 2)-trityl-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-1 (and 2)-trityl-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-amino-1 (and 2)-trityl-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1-trityl-4,4 dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, *J* 7.20 Hz, 3 H) 1.31 (s, 6 H) 2.20 (s, 3 H) 2.43 (m, 4 H) 2.56 (m, 2 H) 2.99 (m, 4 H) 4.24 (q, *J* 7.20 Hz, 2 H) 6.61 (d, *J*=8.79 Hz, 2 H) 6.92-7.37 (m, 17 H) 8.07 (bs, 1 H);

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-2-trityl-4,4 dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J* 7.20 Hz, 3 H) 1.17 (s, 6 H) 2.21 (s, 3 H) 2.46 (m, 4 H) 2.71 (m, 2 H) 3.04 (m, 4 H) 3.40 (q, *J* 7.20 Hz, 2 H) 6.80 (d, *J*=8.79 Hz, 2 H) 6.96-7.43 (m, 15 H) 7.60 (d, *J*=8.79 Hz, 2 H) 8.31 (bs, 1 H) 9.31 (bs, 1 H);

Ethyl 8-anilino-1 (and 2)-trityl-4,4 dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

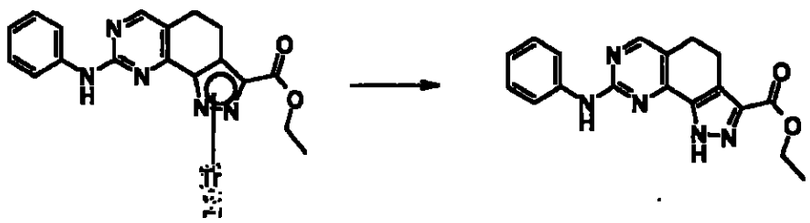
Ethyl 8-amino-1-trityl-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (t, *J*=7.13 Hz, 3 H) 1.31 (s, 6 H) 2.52 (s, 2 H) 4.27 (q, *J*=7.07 Hz, 2 H) 5.20 (s, 2 H) 7.03 - 7.09 (m, 6 H) 7.16 - 7.34 (m, 9 H) 7.93 (s, 1 H);

Ethyl 8-amino-2-trityl-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (t, *J*=7.13 Hz, 3 H) 1.16 (s, 6 H) 2.63 (s, 2 H) 3.46 (q, *J*=7.07 Hz, 2 H) 6.47 (s, 2 H) 7.09 - 7.16 (m, 6 H) 7.24 - 7.41 (m, 9 H) 8.14 (s, 1 H).

Step 5. Ethyl 8-anilino-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X00-M00(C00)-D01]



1.50 g (2.6 mmol) of ethyl 8-anilino-1(2)-trityl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in 50 mL of dichloromethane and 5 mL of trifluoroacetic acid were added. The solution was stirred overnight and the solvent removed in vacuo. The residue was redissolved in dichloromethane and washed with a saturated solution of $NaHCO_3$. The organic layer was then dried over Na_2SO_4 and the solvent evaporated to dryness. By crystallization from diisopropyl ether 0.70 mg of the title compound were obtained (80 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, 3 H, J 7.07 Hz) 3.05-3.28 (2m, 4 H) 4.18 (q, 2 H, J 7.07 Hz) 6.83-7.63 (3m, 5 H) 8.31 (bs, 1 H)9.10 (m, 2 H).

According to the same method the following compounds were prepared:

Ethyl 8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B12-X00-M00(C00)-D01]

Ethyl 8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B13-X00-M00(C00)-D01]

Ethyl 8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B10-X00-M00(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (t, *J* 7.20 Hz, 3H) 2.30 (s, 3 H) 2.50-2.60 (m, 4 H) 2.86 (m, 2 H) 2.99 (m, 2 H) 3.10 (m, 4 H) 4.33 (q, *J* 7.20 Hz, 2 H) 6.90 (d, *J*=8.90 Hz, 2 H) 7.71 (d, *J*=8.90 Hz, 2 H) 8.34 (s, 1H) 9.27 (bs, 1H) 14.22 (bs, 1 H)

Ethyl 8-amino-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X00-M00(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H, J 7.2 Hz) 2.78 (m, 2 H) 2.96 (m, 2 H) 4.31 (q, 2 H, J 7.2 Hz) 6.64 (m, 2 H) 8.19 (bs, 1 H);

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B10-X00-M03(C00)-D01]

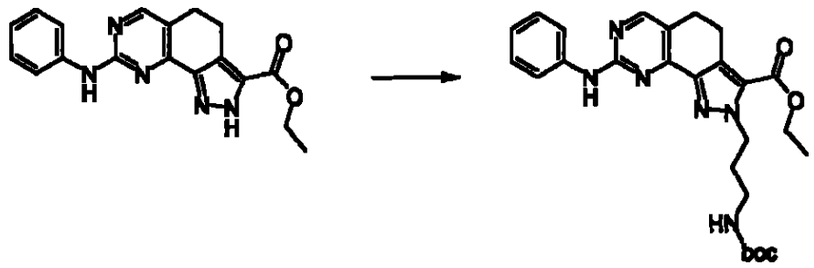
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, *J* 7.20 Hz, 3 H) 1.33 (s, 6 H) 2.22 (s, 3 H) 2.40-2.50 (m, 4 H) 2.73 (m, 2 H) 3.07 (m, 4 H) 4.35 (q, *J* 7.20 Hz, 2 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.70 (d, *J*=9.02 Hz, 2 H) 8.33 (bs, 1 H) 9.30 (bs, 1 H) 14.13 (bs, 1 H);

Ethyl 8-amino-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B00-X00-M03(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.66 (s, 2 H) 4.22 - 4.42 (m, 2 H) 6.36 (d, 2 H) 8.19 (d, 1 H) 14.11 (d, 1 H);

Ethyl 8-anilino-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate [B04-X00-M03(C00)-D01].

<u>Step 6.</u> Ethyl 8-anilino-2-{3-[(tert-butoxycarbonyl)amino]propyl}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate



500 mg of ethyl 8-anilino-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (1.5 mmol) were dissolved in 10 mL of dry dimethylformamide and 1.63 mL of 1 M lithium tert-butoxide in tetrahydrofuran were added to the cooled solution. After 30 minutes under stirring at 0°C a solution of 432 mg of tert-butoxycarbonylaminopropyl bromide in 8 mL of dry tetrahydrofuran were added dropwise. After a night at room temperature the mixture was poured into a solution of NaH_2PO_4 and extracted with

dichloromethane. The organic layer was then dried over Na_2SO_4 and the solvent evaporated, giving an oil that was treated according to the following step 7, without any further purification.

Analogously the following compounds can be prepared:

Ethyl 2-{3-[(tert-butoxycarbonyl)amino]propyl}-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 2-{3-[(tert-butoxycarbonyl)amino]propyl}-8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 2-{3-[(tert-butoxycarbonyl)amino]propyl}-8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-amino-2-{3-[(tert-butoxycarbonyl)amino]propyl}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

Ethyl 8-amino-2-{3-[(tert-butoxycarbonyl)amino]propyl}-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3- h]quinazoline-3-carboxylate;

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-2-{3-[(tert-butoxycarbonyl)amino]propyl}-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

Ethyl 8-anilino-2-{3-[(tert-butoxycarbonyl)amino]propyl}-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3- h]quinazoline-3-carboxylate.

Following the above method, but employing tert-butoxycarbonylaminoethyl bromide, the following compounds were prepared:

Ethyl 8-anilino-2-{2-[(tert-butoxycarbonyl)amino]ethyl}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

Ethyl 2-{2-[(tert-butoxycarbonyl)amino]ethyl}-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 2-{2-[(tert-butoxycarbonyl)amino]ethyl}-8-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 2-{2-[(tert-butoxycarbonyl)amino]ethyl}-8-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

Ethyl 8-amino-2-[2-[(tert-butoxycarbonyl)amino]ethyl]-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate

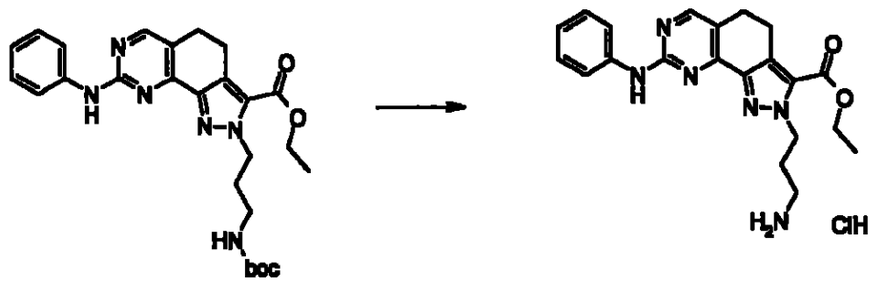
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 9H) 1.36 (t, 3 H, J 7.2 Hz) 2.74 (m, 2 H) 2.94 (m, 2 H) 3.34 (m, 2 H) 4.33 (q, 2 H, J 7.2 Hz) 4.57 (t, 2 H) 6.50 (m, 2 H) 6.87 (t, 1 H) 8.15 (bs, 1 H);

Ethyl 8-amino-2-[2-[(tert-butoxycarbonyl)amino]ethyl]-4,4-dimethyl-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]- 2-[2-[(tert-butoxycarbonyl)amino]ethyl]-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate;

Ethyl 8-anilino-2-[2-[(tert-butoxycarbonyl)amino]ethyl]-4,4-dimethyl-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate.

Step 7. Ethyl 2-(3-aminopropyl)-8-anilino-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride [B04-X00-M04(C13)-D01]



The crude of previous step 6 was dissolved in 20 mL of dioxane and 8 mL of HCl 37% were added. After 6 hours under stirring at room temperature the solvent was removed in vacuo, the residue triturated with ethanol and the product collected by filtration (80 % yield).

By working according to the above method, the following compounds were prepared:

B04-X00-M04(C12)-D01

B00-X00-M04(C12)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (t, 3 H, J 7.2 Hz) 2.85 (m, 2 H) 3.02 (m, 2 H) 3.50 (m, 2 H) 4.37 (q, 2 H, J 7.2 Hz) 4.84 (t, 2 H) 7.47 (m, 1 H) 8.08 (m, 3 H) 8.29 (s, 1 H);

B12-X00-M04(C12)-D01
B13-X00-M04(C12)-D01

B10-X00-M04(C12)-D01
B12-X00-M04(C13)-D01
B13-X00-M04(C13)-D01
B10-X00-M04(C13)-D01

Ethyl 8-amino-2-(3-aminopropyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B00-X00-M04(C13)-D01;

Ethyl 8-amino-2-(3-aminopropyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B00-X00-M09(C13)-D01;

Ethyl 2-(3-aminoprepyl)-8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B10-X00-M09(C13)-D01;

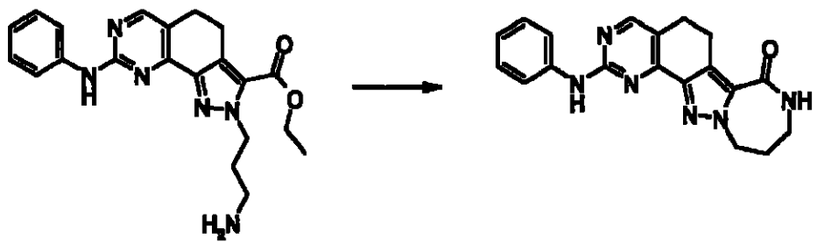
Ethyl 8-anilino-2-(3-aminopropyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B04-X00-M09(C13)-D01;

Ethyl 8-amino-2-(3-aminoethyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B00-X00-M09(C12)-D01;

Ethyl 2-(3-aminoethyl)-8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B10-X00-M09(C12)-D01;

Ethyl 8-anilino-2-(3-aminoethyl)-4,4-dimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride B04-X00-M09(C12)-D01.

Step 8, 2-anilino-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B04-X00-M06]



185 mg (0.43 mmol) of ethyl 2-(3-aminopropyl)-8-anilino-4,5-dihydro-2 H-pyrazolo[4,3-h]quinazoline-3-carboxylate hydrochloride were dissolved in 10 mL of methanol and 400 mg of cesium carbonate were added. After 3 hours under stirring at room temperature the solvent was removed at reduced pressure. Water was then added to the residue and the solid collected by filtration and washed with water and acetone to give 100 mg (70% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (ddd, *J* 13.02, 6.65, 6.55 Hz, 2 H) 2.88 (m, 4 H) 3.21 (q, *J* 5.89 Hz, 2 H) 4.50 (t, *J* 6.77 Hz, 2 H) 6.93 (t, *J* 7.32 Hz, 1 H) 7.28 (dd, *J* 8.29, 7.56 Hz, 2 H) 7.85 (d, *J* 7.68 Hz, 2 H) 8.27 (t, *J* 5.18 Hz, 1 H) 8.38 (s, 1 H) 9.62 (s, 1 H)

By working according to this method the following compounds were prepared:

2-anilino-5,6,9,10-tetrahydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B04-X00-M05]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 (m, 4 H) 3.65 (m, 2 H) 4.41 (m, 2 H) 6.93 (m, 1 H) 7.28 (m, 2 H) 7.85 (m, 2 H) 8.26 (m, 1 H) 8.39 (s, 1 H) 9.61 (s, 1 H);

2-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-5,6,9,10-tetrahydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B12-X00-M05]

2-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-5,6,9,10-tetrahydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B13-X00-M05]

2-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-5,6,9,10-tetrahydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one[B10-X00-M05]

2-amino-5,6,9,10-tetrahydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B00-X00-M05]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, *J*=7.56 Hz, 2 H) 2.88 - 2.98 (m, 2 H) 3.60 - 3.68 (m, 2 H) 4.29 - 4.42 (m, 2 H) 6.48 (s, 2 H) 8.15 (s, 1 H) 8.21 - 8.32 (m, 1 H);

2-amino-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one[B00-X00-M06]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (ddd, *J* 13.02, 6.65, 6.55 Hz, 2 H) 2.74 (m, 2 H) 2.92 (m, 2 H) 3.21 (q, *J* 5.89 Hz, 2 H) 4.50 (t, *J* 6.77 Hz, 2 H) 6.48 (m, 2 H) 8.17 (s, 1 H) 8.23 (m, 1 H);

2-{[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]amino}-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one[B12-X00-M06]

2-{[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]amino}-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B13-X00-M06]

2-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-5,6,8,9,10,11-hexahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B10-X00-M06]

2-amino-6,6-dimethyl-5,9,10-trihydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B00-X00-M07];

2-anilino-6,6-dimethyl-5,9,10-trihydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B04-X00-M07];

2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-6,6-dimethyl-5,9,10-trihydropyrazino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7(8H)-one [B10-X00-M07]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.92 (m, 2 H) 3.07 (m, 4 H) 3.65 (m, 2 H) 4.41 (m, 2 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.23 (m, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H);

2-amino-6,6-dimethyl-5,8,9,10,11-pentahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B00-X00-M08];

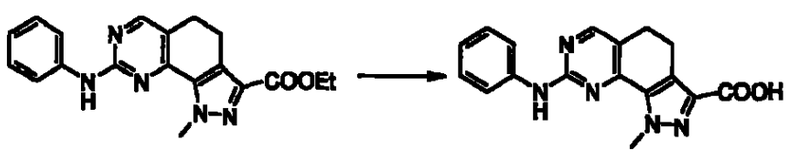
2-anilino-6,6-dimethyl-5,8,9,10,11-pentahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B04-X00-M08];

2-[4-(4-methyl-piperazin-1-yl)-phenylamino]-6,6-dimethyl-5,8,9,10,11-pentahydro-7H-[1,4]diazepino[1',2':1,5]pyrazolo[4,3-h]quinazolin-7-one [B10-X00-M08]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.18 (ddd, *J* 13.02, 6.65, 6.55 Hz, 2 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.92 (m, 2 H) 3.07 (m, 4 H) 3.21 (q, *J* 5.89 Hz, 2 H) 4.50 (t, *J* 6.77 Hz, 2 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.27 (m, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H).

Example 50

8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid [B04-X00-M00(C01)-D02]



0.63 g (1.80 mmol) of ethyl 8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate were dissolved in 100 mL of a mixture tetrahydrofuran/methanol/water 8/1/1 and 0.19 g (4,53 mmol) of lithium hydroxide hydrate were added. The solution was stirred at 60°C for 1.5 hours. The mixture was then cooled to room temperature and 1 N HCl added until neutral pH. Water was added and the resulting precipitate collected by filtration (87% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (t, *J* 7.74 Hz, 2 H) 2.99 (m, 2 H) 4.36 (s, 3 H) 6.98 (tt, *J* 7.35, 1.07 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.50 Hz, 2 H) 7.72 (dd, *J* 8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.52 (s, 1 H) 12.68 (s, 1 H)

By working according to the same procedure the following compounds were prepared:

B00-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.48 and 3.64 (2t, *J* 7.25 Hz, 4 H) 3.84 (s, 3 H) 8.04 (bs, 2 H) 8.46 (bs, 1 H);

B09-X00-M00(C03)-D02

^{1}H NMR (400 MHz, DMSO-d_6 Hz) 6.49 (m, 1 H) 7.07 (m, 2 H) 7.94 (bs, 1 H) 8.30 (s, 1 H) 9.35 (bs, 1 H);

B09-X00- M04(C03)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 9H) 1.62 (m, 2 H) 2.26 (s, 3 H) 2.52 (m, 4 H) 3.13 (m, 4 H) 4.86 (m, 2 H) 6.58 (m, 1 H) 7.13 (m, 1 H) 7.20 (m, 1 H) 8.41 (s, 1 H) 9.20 (bs, 1 H);

B10-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (s, 3 H) 2.74 (m, 2 H) 2.95 (m, 2 H) 4.30 (s, 3 H) 6.93 (m, 2 H) 7.52 (m, 2 H) 8.33 (s, 1 H) 9.28 (bs, 1 H);

B103-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 (m, 4 H) 2.83 (m, 5 H) 2.97 (t, 2 H) 4.33 (s, 3 H) 7.02 (m, 2 H) 7.61 (m, 2 H) 8.38 (s, 1 H) 9.39 (s, 1 H);

B09-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (m, 5 H) 2.93 (t, 2 H) 3.09 (m, 4 H) 3.71 (m, 4 H) 4.32 (s, 3 H) 6.64 (m, 1 H) 7.17 (m, 1 H) 7.29 (m, 2 H) 8.38 (s, 1 H) 9.42 (s, 1 H) 10.33 (s, 1 H);

B04-X04-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.89 (t, 2 H) 2.97 (t, 2 H) 3.70 (s, 3 H) 7.51 (m, 3 H) 7.67 (m, 2 H) 8.56 (s, 1 H) 12.81 (bs, 1 H);

B05-X06-M00(C01)-D02

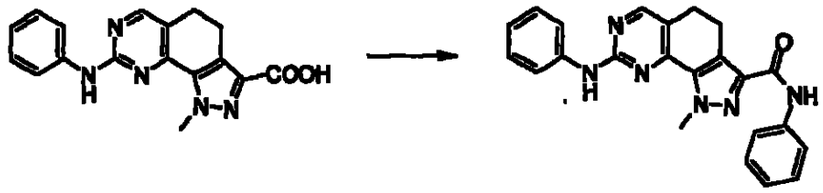
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 (t, 2 H) 2.97 (t, 2 H) 4.23 (s, 2 H) 4.26 (s, 3 H) 7.23 (m, 1 H) 7.32 (m, 2 H) 7.36 (m, 2 H) 8.65 (s, 1 H) 12.82 (bs, 1 H);

B10-X00-M04(C15)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.60 (m, 5 H) 2.89 (m, 2 H) 3.04 (m, 4 H) 3.33 (m, 4 H) 6.31 (s, 2 H) 6.78 (d, 2 H) 7.39 (m, 3 H) 7.47 (m, 2 H) 7.63 (m, 2 H) 7.67 (s, 1 H) 8.42 (s, 1 H) 9.33 (s, 1 H) 13.55 (s, 1 H).

Example 51

8-anilino-1-methyl-N-phenyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B04-X00-M00(C01)-D20]



45 mg (0.14 mmol) of 8-anilino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid were dissolved in 7 mL of dimethylformamide and 145.6 mg (0.28 mmol) of (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP); 0.12 mL (0.70 mmol) of N,N-diisopropyl-N-ethyl amine and 0.08 mL (0.70 mmol) of aniline were then added. After 6 hours the solvent was removed, the residue was redissolved with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The product crystallized from methanol (60% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.88 (m, 2 H) 3.07 (m, 2 H) 4.43 (s, 3 H,) 6.97-7.85 (6m, 10H) 8.45 (s, 1 H) 9.55 (s, 1 H) 10.09 (s, 1 H).

By working analogously the following compounds were prepared:

Table XIII

B04-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, *J*=4.76 Hz, 3 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, *J*=7.38 Hz, 1 H) 7.21 - 7.32 (m, 2 H) 7.68 (d, *J*=7.56 Hz, 2 H) 8.06 (q, *J*=4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H)
B04-X00-M00(C01)-D08	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (m, 4 H) 2.83 (m, 2 H) 2.94 (m, 2 H) 3.49 (t, *J* 6.77 Hz, 2 H) 3.83 (t, *J* 6.58 Hz, 2 H) 4.34 (s, 3 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (dd, *J* 8.29, 7.56 Hz, 2 H) 7.73 (d, *J* 7.44 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B04-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 (m, 2 H) 3.01 (m, 2 H) 4.36 (s, 3 H) 4.43 (d, *J* 6.34 Hz, 2 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (m, 7 H) 7.72 (d, *J* 7.5 Hz, 2 H) 8.42 (s, 1 H) 8.71 (t, *J* 6.4 Hz, 1 H) 9.52 (s, 1 H)

B04-X00-M00(C01)-D10	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65-3.5 (m, 15 H) 4.35 (s, 3 H) 6.98 (t, *J* 7.4 Hz, 1 H) 7.32 (dd, *J* 8.29, 7.56 Hz, 2 H) H) 7.73 (d, *J* 7.5 Hz, 2 H) 8.44 (s, 1 H) 9.55 (s, 1 H)
B04-X00-M00(C01)-D11	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (d, *J* 6.71 Hz, 6 H) 1.86 (m, 1 H) 2.83 (dd, *J* 8.05, 7.19 Hz, 2 H) 3.00 (t, *J* 7.74 Hz, 2 H) 3.07 (t, *J* 6.58 Hz, 2 H) 4.36 (s, 3 H) 6.97 (tt, *J* 7.32, 1.10 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.50 Hz, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.09 (t, *J* 6.16 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D12	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 3.01 (m, 2 H) 3.28 (s, 3 H) 3.43 (m, 4 H) 4.36 (s, 3 H) 6.98 (m, 1 H) 7.31 (dd, *J* 8.41, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 7.99 (t, *J* 5.49 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D13	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (m, 6 H) 1.83 (m, 2 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 2.9-3.5 (m, 8 H) 4.36 (s, 3 H) 6.97 (m, 1 H) 7.31 (m, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.09 (t, *J* 6.16 Hz, 1 H) 8.43 (s, 1 H) 9.53 (s, 1 H)
B04-X00-M00(C01)-D14	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 4 H) 1.70 (m, 2 H) 1.85 (m, 2 H) 2.83 (m, 2 H) 3.0 (m, 2 H) 4.21 (m, 1 H) 4.35 (s, 3 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (dd, *J* 8.29, 7.56 Hz, 2 H) 7.73 (d, *J* 7.44 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B04-X00-M00(C01)-D15	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 (s, 3 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 3.06 (m, 8 H) 4.42 (s, 3 H) 6.75 (m, 1 H) 6.99 (t, *J* 7.32 Hz, 1 H) 7.20 (t, *J* 8.05 Hz, 1 H) 7.32 (m, 3 H) 7.55 (bs, 1 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.45(s, 1 H) 9.55 (s, 1 H) 9.91 (s, 1 H)
B04-X00-M00(C01)-D16	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (m, 2 H) 3.01 (m, 2 H) 4.35 (s, 3 H) 4.43 (d, *J* 6.10 Hz, 2 H) 6.25 (dd, *J* 3.17, 0.85 Hz, 1 H) 6.40 (dd, *J* 3.17, 1.83 Hz, 1 H) 6.97 (m, 1 H) 7.31 (dd, *J* 8.54, 7.44 Hz, 2 H) 7.57 (dd, *J* 1.83, 0.85 Hz, 1 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.42 (s, 1 H) 8.54 (t, *J* 6.04 Hz, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D17	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.7 (m, 2 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 3.2-3.7 (m, 12 H) 4.35 (s, 3 H) 6.98 (m, 1 H) 7.32 (dd, *J* 8.54, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.38 (m, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B00-X00-M00(C21)-D04]	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (d, *J*=10.73 Hz, 2 H) 2.11 - 2.31 (m, 4 H) 2.70 (t, *J*=7.93 Hz, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.86 - 3.02 (m, *J*=7.56, 7.56 Hz, 4 H) 3.55 (s, 2 H) 5.50 - 5.62 (m, 1 H) 6.51 (s, 2 H) 7.19 - 7.39 (m, 5 H) 7.93 - 8.04 (m, 1 H) 8.17 (s, 1 H)
B00-X00-M00(C01)-D18	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 3.03

	(m, 2 H) 4.40 (s, 3 H) 6.61 (bs, 2 H) 7.18 (m, 1 H) 7.87 (m, 1 H) 8.18 (m, 1 H) 8.22 (m, 1 H) 8.37 (m, 1 H) 9.46 (s, 1 H).
B04-X00-M00(C01)-D27	
B04-X00-M04(C01)-D27	
B04-X00-M00(C21)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 (d, *J*=9.76 Hz, 2 H) 2.00 - 2.10 (m, 2 H) 2.13 - 2.28 (m, 2 H) 2.81 (t, *J*=7.44 Hz, 2 H) 2.88 (d, *J*=11.22 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.51 (s, 2 H) 4.42 - 4.50 (m, *J*=6.46 Hz, 2 H) 5.49 - 5.62 (m, 1 H) 6.99 - 7.40 (m, 13 H) 7.61 (d, *J*=8.66 Hz, 2 H) 8.42 (s, 1 H) 8.68 (t, *J*=6.16 Hz, 1 H) 9.44 (s, 1 H)
B04-X00-M00(C01)-D19	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 4 H) 3.01 (m, 2 H) 3.49 (m, 2 H) 4.35 (s, 3 H) 6.97 (m, 1 H) 7.31 (m, 7 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.18 (m, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B10-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (d, *J*=4.76 Hz, 3 H) 2.81 (t, *J*=7.68 Hz, 2 H) 2.85 (d, *J*=4.39 Hz, 3 H) 2.94 - 3.07 (m, 4 H) 3.11 - 3.25 (m, 2 H) 3.51 (d, *J*=11.83 Hz, 2 H) 3.73 (d, *J*=13.66 Hz, 2 H) 4.33 (s, 3 H) 6.99 (d, *J*=9.15 Hz, 2 H) 7.60 (d, *J*=9.02 Hz, 2 H) 8.08 (q, *J*=4.67 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H) 10.36 (s, 1 H)
B10-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.29 (s, 3 H) 2.55 (m, 4 H) 2.80 (m, 2 H) 2.99 (m, 2 H) 3.10 (m, 2 H) 4.34 (s, 3 H) 4.44 (d, *J* 6.34 Hz, 2 H) 6.92 (d, *J* 9.02 Hz, 2 H) 7.25 (m, 1 H) 7.32 (m, 4 H) 7.72 (d, *J* 7.5 Hz, 2 H) 8.35 (s, 1 H) 8.69 (t, *J* 6.4 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 3.34 (m, 4 H), 4.34 (s, 3 H), 4.40 (d, 2 H), 6.93 (d, 2 H), 7.15 (t, 2 H), 7.37, (t, 2 H), 7.53 (d, 2 H), 8.35 (s, 1 H), 8.74 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D22	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 3.34 (m, 4 H), 3.74, (s, 3 H), 4.33 (d+s, 5 H), 6.90 (t, 4 H), 7.25 (d, 2 H), 7.53 (d, 2 H), 8.35 (s, 1 H), 8.60 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D23	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.52 (m, 4 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 4.35 (s, 3 H), 4.50 (d, 2 H), 6.93 (d, 2 H), 7.55 (m, 4 H), 7.69 (d, 2 H), 8.35 (s, 1 H), 8.87 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D24	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H), 2.24 (s, 3 H), 2.47 (m, 4 H), 2.78 (t, 2 H), 2.96 (t, 2 H), 3.08 (m, 4 H), 4.35 (s, 3 H), 5.15 (m, 1 H), 6.91 (d, 2 H), 7.24 (m, 1 H), 7.33 (t, 2 H), 7.42 (m, 2 H), 7.53 (d, 2 H), 8.34 (s, 1 H), 8.43 (d, 1 H), 9.25 (s, 1 H).
B10-X00-M00(C19)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 2.24

	(s, 3 H) 2.48 (m, 4 H) 3.12 (m, 4 H) 5.44 (m, 1 H) 6.95 (m, 2 H) 7.38 (m, 2 H) 7.94 (s, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H).
B10-X00-M00(C01)-D40	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.80 (t, 2 H) 2.99 (t, 3 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 4.43 (d, 2 H) 6.93 (d, 2 H) 7.07 (m, 1 H) 7.14 (m, 1 H) 7.18 (m, 1 H) 7.37 (m, 1 H) 7.53 (d, 2 H) 8.35 (m, 1 H) 8.79 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D16	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 (m, 15 H) 4.33 (s, 3 H) 4.43 (d, *J*=5.97 Hz, 2 H) 6.25 (dd, *J*=3.17, 0.85 Hz, 1 H) 6.40 (dd, *J*=3.23, 1.89 Hz, 1 H) 6.94 (d, *J*=9.02 Hz, 2 H) 7.56 (d, *J*=9.02 Hz, 2 H) 7.57 (dd, *J*=1.83, 0.85 Hz, 1 H) 8.36 (s, 1 H) 8.52 (t, *J*=6.16 Hz, 1 H) 9.29 (s, 1 H)
B10-X00-M00(C01)-D76	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 12 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.59 (m, 4 H) 4.33 (s, 3 H) 6.92 (d, 2 H) 7.52 (d, 2 H) 7.99 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D47	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.64 (m, 4 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.13 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.54 (d, 2 H) 8.34 (s, 1 H) 8.42 (d, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D61	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (d, 3 H) 2.27 (s, 3 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.52 (d, 2 H) 8.34 (s, 1 H) 8.42 (d, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D50	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.60 (s, 3 H) 4.32 (s, 3 H) 4.39 (d, 2 H) 5.89 (m, 1 H) 5.97 (m, 1 H) 6.64 (m, 1 H) 6.92 (d, 2 H) 7.52 (d, 2 H) 8.26 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.49 (m, 4 H) 2.82 (t, 2 H) 3.01 (t, 2 H) 3.10 (m, 4 H) 4.38 (s, 3 H) 4.46 (d, 2 H) 6.94 (d, 2 H) 7.33 (d, 2 H) 7.55 (d, 2 H) 8.37 (s, 1 H) 8.52 (d, 2 H) 8.88 (t, 1 H) 9.29 (s, 1 H)
B10-X00-M00(C01)-D45	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.09 (m, 4 H) 4.34 (s, 3 H) 4.44 (d, 2 H) 6.93 (d, 2 H) 7.38 (m, 1 H) 7.53 (d, 2 H) 7.72 (m, 1 H) 8.35 (s, 1 H) 8.46 (m, 1 H) 8.55 (m, 1 H) 8.83 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (m, 3 H) 2.53 (m, 4 H) 2.78 (m, 2 H) 2.94 (m, 2 H) 3.10 (m, 4 H) 3.74 (m, 2 H) 4.37 (m, 3 H) 5.00 (t, 1 H) 5.03 (m, 1 H) 6.92 (m, 2 H) 7.25 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.54 (m, 2 H) 8.27 (d, 1 H) 8.34 (m, 1 H) 9.26 (m, 1 H)

B10-X00-M00(C01)-D60	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, *J*=7.74 Hz, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 3.74 (m, 2 H) 4.37 (s, 3 H) 5.01 (m, 2 H) 6.92 (d, 2 H) 7.30 (m, 5 H) 7.53 (d, 2 H) 8.27 (d, *J*=8.29 Hz, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D42	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (s, 2 H) 3.09 (m, 4 H) 4.34 (s, 3 H) 4.39 (d, 2 H) 6.93 (d, 2 H) 7.18 (m, 1 H) 7.37 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.81 (t, 1 H) 9.26 (m, 1 H)
B10-X00-M00(C01)-D41	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J*=7.32 Hz, 3 H) 1.87 (m, 2 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.77 (m, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 4.88 (td, *J*=8.75, 6.40 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.23 (m, 1 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.42 (m, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.78 Hz, 2 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D54	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.52 (m, 10 H) 2.78 (t, 2 H) 2.95 (m, 4 H) 3.08 (m, 4 H) 3.59 (m, 4 H) 4.37 (s, 3 H) 5.16 (m, 1 H) 6.92 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, 2 H) 8.34 (s, 1 H) 8.40 (d, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D67	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H) 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 3.66 (s, 3 H) 4.30 (d, *J*=5.97 Hz, 2 H) 4.32 (s, 3 H) 5.94 (s, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.23 (t, *J*=5.97 Hz, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D49	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 3.00 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 4.33 (s, 3 H) 4.58 (d, *J*=6.22 Hz, 2 H) 6.91 (d, *J*=9.02 Hz, 2 H) 6.96 (dd, *J*=5.06, 3.48 Hz, 1 H) 7.01 (dd, *J*=3.41, 1.10 Hz, 1 H) 7.37 (dd, *J*=5.06, 1.28 Hz, 1 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.74 (t, *J*=6.22 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D68	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J*=7.26 Hz, 3 H) 1.86 (m, 2 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.78 (m, 2 H) 2.95 (m, 2 H) 3.08 (m, 4 H) 4.35 (s, 3 H) 4.88 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.78 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D64	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.83 (m, 4 H) 2.90 (m, 3 H) 3.09 (m, 4 H) 3.18 (s, 3 H) 4.30 (d, *J*=17.68 Hz, 6 H) 4.69 (s, 2 H) 4.97 (s, 2 H) 6.91 (m, *J*=9.02 Hz, 2 H) 7.29 (m, 5 H) 7.52 (m, 2 H) 8.36 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D53	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m,

	4 H) 4.37 (s, 3 H) 5.13 (m, 1 H) 6.93 (d, 2 H) 7.41 (d, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.51 (m, 2 H) 8.66 (d, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (s, 6 H) 2.26 (s, 3 H) 2.50 (m, 4 H) 2.79 (t, 2 H) 2.92 (t, 2 H) 3.10 (m, 4 H) 4.38 (s, 3 H) 6.94 (d, 2 H) 7.22 (m, 1 H) 7.34 (m, 2 H) 7.43 (m, 2 H) 7.54 (d, 2 H) 7.81 (s, 1 H) 8.36 (s, 1 H) 9.28 (s, 1 H)
B10-X00-M00(C01)-D57	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, 2 H) 3.01 (t, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 4.92 (d, 2 H) 6.92 (d, 2 H) 7.57 (m, 6 H) 7.85 (m, 1 H) 7.96 (m, 1 H) 8.24 (m, 1 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D59	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.09 (m, 4 H) 4.32 (d, *J*=5.85 Hz, 2 H) 4.33 (s, 3 H) 5.98 (s, 2 H) 6.80 (dd, *J*=7.93, 1.59 Hz, 1 H) 6.86 (d, *J*=7.80 Hz, 1 H) 6.91 (d, *J*=2.56 Hz, 1 H) 6.91 (d, *J*=8.05 Hz, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.63 (t, *J*=6.40 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (d, *J*=7.07 Hz, 3 H) 2.27 (s, 3 H) 2.51 (m, 4 H) 2.78 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.74 Hz, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.15 (t, *J*=8.96 Hz, 2 H) 7.46 (dd, *J*=8.54, 5.61 Hz, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.49 (d, *J*=8.41 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D74	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (m, 2 H) 1.18 (m, 4 H) 1.67 (m, 5 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, 2 H) 2.98 (t, 2 H) 3.08 (m, 6 H) 4.33 (s, 3 H) 6.92 (d, 2 H) 7.53 (d, 2 H) 8.05 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (m, 4 H) 2.24 (s, 3 H) 2.52 (m, 8 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.08 (m, 4 H) 4.36 (s, 3 H) 5.11 (m, 1 H) 6.92 (d, 2 H) 7.33 (m, 3 H) 7.41 (m, 2 H) 7.52 (d, 2 H) 8.34 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, *J*=7.80 Hz, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.53 (d, *J*=7.80 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.38 (m, 1 H) 7.47 (m, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 7.86 (s, 1 H) 8.12 (d, *J*=7.80 Hz, 1 H) 8.35 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.53 (m, 10 H) 2.80 (t, 2 H) 2.95 (m, 4 H) 3.10 (m, 4 H) 3.58 (m, 4 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 6.94 (d, 2 H) 7.26 (m, 1 H) 7.35 (m, 2 H) 7.44 (m, 2 H) 7.55 (d, 2 H) 8.36 (s, 1 H) 8.42 (d, 1 H) 9.28 (s, 1 H)
B10-X00-M00(C01)-D62	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.98 (t, *J*=7.56 Hz, 2 H)

	3.09 (m, 4 H) 4.35 (s, 3 H) 6.36 (d, *J*=8.78 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.28 (m, 2 H) 7.36 (t, *J*=7.50 Hz, 4 H) 7.41 (m, 4 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.70 (d, *J*=8.90 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D75	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 11 H) 1.12 (d, *J*=6.83 Hz, 3 H) 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.62 Hz, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 3.82 (m, 1 H) 4.33 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 7.65 (d, *J*=9.27 Hz, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D46	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.50 (m, 4 H) 2.78 (t, *J*=7.80 Hz, 2 H) 2.96 (m, 2 H) 3.09 (m, 4 H) 3.30 (s, 3 H) 3.60 (dd, *J*=9.94, 5.18 Hz, 1 H) 3.78 (dd, *J*=10.00, 7.93 Hz, 1 H) 4.37 (s, 3 H) 5.23 (m, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.30 (m, 3 H) 7.43 (m, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.54 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D56	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 (m, 6 H) 2.04 (m, 4 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.78 (t, *J*=7.68 Hz, 2 H) 2.91 (t, *J*=7.80 Hz, 2 H) 3.08 (m, 4 H) 4.37 (s, 3 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.28 (m, 5 H) 7.42 (s, 1 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D69	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.86 (m, 4 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.77 (m, 2 H) 2.83 (t, *J*=7.68 Hz, 2 H) 3.03 (m, 2 H) 3.08 (m, 4 H) 4.31 (s, 3 H) 5.20 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.16 (m, 4 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.14 (d, *J*=9.02 Hz, 1 H) 8.36 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D63	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 3.15 (t, *J*=8.66 Hz, 2 H) 4.33 (m, 2 H) 4.33 (s, 3 H) 4.50 (t, *J*=8.72 Hz, 2 H) 6.69 (d, *J*=8.17 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.05 (dd, *J*=8.11, 1.89 Hz, 1 H) 7.20 (d, *J*=1.22 Hz, 1 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 8.56 (t, *J*=6.34 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D65	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.60 (m, 4 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.93 (m, 4 H) 3.08 (m, 4 H) 4.32 (s, 3 H) 5.52 (q, *J*=8.17 Hz, 1 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.24 (m, 4 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.27 (d, *J*=8.66 Hz, 1 H) 8.36 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (m, 4 H) 2.26 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 6.93 (d, 2 H) 7.16 (m, 1 H) 7.25 (m, *J*=10.00 Hz, 4 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.86 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D66	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 (s, 6 H) 2.24 (s, 3 H) 2.50 (m, 4 H) 2.76 (t, 2 H) 2.88 (t, 2 H) 3.08 (m,

	4 H) 4.37 (s, 3 H) 6.93 (d, 2 H) 7.37 (m, 2 H) 7.52 (d, 2 H) 8.04 (s, 1 H) 8.33 (s, 1 H) 8.48 (m, 2 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D55	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 4.35 (s, 3 H) 4.48 (d, 2 H) 6.93 (d, 2 H) 7.18 (m, 2 H) 7.31 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.68 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.75 (s, 3 H) 4.34 (s, 3 H) 4.39 (d, 2 H) 6.83 (m, 1 H) 6.90 (m, 4 H) 7.24 (t, 1 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.67 (t, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D48	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.47 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.85 (s, 3 H) 4.35 (s, 3 H) 4.41 (d, 2 H) 6.92 (m, 3 H) 7.01 (m, 1 H) 7.17 (m, 1 H) 7.24 (m, 1 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.38 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D77	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J*=7.56 Hz, 6 H) 2.29 (s, 3 H) 2.55 (m, 4 H) 2.56 (q, *J*=7.68 Hz, 4 H) 2.83 (t, *J*=7.62 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.11 (m, 4 H) 4.40 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.14 (d, *J*=7.68 Hz, 2 H) 7.22 (dd, *J*=8.29, 6.83 Hz, 1 H) 7.56 (d, *J*=9.02 Hz, 2 H) 8.37 (s, 1 H) 9.28 (s, 1 H) 9.57 (s, 1 H)
B10-X00-M00(C01)-D58	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.74 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.08 (m, 4 H) 3.73 (s, 6 H) 4.34 (s, 3 H) 4.36 (d, *J*=6.71 Hz, 2 H) 6.38 (t, *J*=2.32 Hz, 1 H) 6.50 (d, *J*=2.19 Hz, 2 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.64 (t, *J*=6.28 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D20	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.84 (t, *J*=7.74 Hz, 2 H) 3.05 (t, *J*=7.74 Hz, 2 H) 3.09 (m, 4 H) 4.41 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.10 (tt, *J*=7.39, 1.14 Hz, 1 H) 7.34 (dd, *J*=8.29, 7.56 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 7.83 (dd, *J*=8.66, 1.10 Hz, 2 H) 8.38 (s, 1 H) 9.28 (s, 1 H) 10.07 (s, 1 H)
B10-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.27 (s, 3 H) 2.52 (m, 10 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.12 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.53 (d, 2 H) 8.34 (m, 2 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D70	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.79 (t, 2 H) 2.97 (t, 2 H) 3.09 (m, 4 H) 3.35 (m, 4 H) 3.65 (dd, 1 H) 3.90 (dd, 1 H) 4.37 (s, 3 H) 5.25 (m, 1 H) 6.92 (d, *J*=8.78 Hz, 2 H) 7.29 (m, 1 H) 7.37 (m, 2 H) 7.47 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.82 (d, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D73	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.81 (m, 4 H) 3.11 (m, 6 H) 3.34 (m, 4 H) 4.33 (s, 3 H) 4.52 (m, 1 H) 5.38 (m, 1 H) 5.44 (d, 1 H) 6.92 (d, 2 H) 7.22

	(m, 3 H) 7.53 (d, 2 H) 7.70 (m, 1 H) 8.38 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D165	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.74 (t, 2 H) 2.87 (t, 2 H) 3.09 (m, 4 H) 3.35 (m, 8 H) 4.34 (s, 3 H) 6.92 (d, 2 H) 7.31 (m, 1 H) 7.43 (m, 4 H) 7.52 (d, 2 H) 8.32 (s, 1 H) 9.10 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D144	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (s, 3 H) 2.24 (m, 7 H) 2.47 (m, 4 H) 2.78 (m, 6 H) 3.08 (m, 4 H) 3.46 (m, 2 H) 3.55 (m, 2 H) 4.37 (s, 3 H) 6.93 (d, 2 H) 7.21 (m, 1 H) 7.35 (m, 4 H) 7.54 (d, 2 H) 8.35 (m, 2 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D164	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 3.55 (m, 8 H) 4.34 (s, 3 H) 6.00 (d, 1 H) 6.92 (d, 2 H) 7.34 (m, 1 H) 7.43 (m, 4 H) 7.52 (d, 2 H) 8.24 (d, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B109-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.53 (m, 4 H) 2.83 (m, 2 H) 3.00 (m, 6 H) 4.36 (s, 3 H) 4.44 (d, *J*=6.34 Hz, 2 H) 7.01 (dd, *J*=9.94, 8.96 Hz, 1 H) 7.27 (m, 5 H) 7.37 (dd, *J*=8.29, 2.19 Hz, 1 H) 7.67 (dd, *J*=15.36, 2.44 Hz, 1 H) 8.41 (s, 1 H) 8.71 (t, *J*=6.34 Hz, 1 H) 9.55 (s, 1 H)
B109-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.54 (m, 4 H) 2.82 (t, *J*=7.68 Hz, 2 H) 2.99 (m, 6 H) 4.36 (s, 3 H) 4.41 (d, *J*=6.34 Hz, 2 H) 7.01 (dd, *J*=9.94, 8.96 Hz, 1 H) 7.15 (t, *J*=8.96 Hz, 2 H) 7.37 (m, 3 H) 7.67 (dd, *J*=15.43, 2.38 Hz, 1 H) 8.41 (s, 1 H) 8.75 (t, *J*=6.28 Hz, 1 H) 9.55 (s, 1 H)
B108-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 2.71 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.34 (s, 3 H) 6.91 (d, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.51 d, 2 H) 8.34 (s, 1 H) 9.24 (s, 1 H)
B108-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 9 H) 2.71 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.34 (s, 3 H) 4.42 (d, 2 H) 6.91 (d, 2 H) 7.34 (m, 5 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.24 (s, 1 H)
B108-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 2.69 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.36 (s, 3 H) 4.44 (d, 2 H) 6.92 (d, 2 H) 7.31 (m, 2 H) 7.54 (d, 2 H) 8.35 (s, 1 H) 8.50 (m, 2 H) 8.86 (t, 1 H) 9.26 (s, 1 H)
B108-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 1.70 (s, 6 H) 2.69 (m, 4 H) 2.77 (t, 2 H) 2.90 (t, 2 H) 3.06 (m, 4 H) 4.36 (s, 3 H) 6.92 (d, 2 H) 7.20 (m, 1 H) 7.32 (m, 2 H) 7.41 (m, 2 H) 7.51 (d, 2 H) 7.79 (s, 1 H) 8.33 (s, 1 H) 9.25 (s, 1 H)
B108-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (s, 9 H) 2.69

	(s, 4 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.86 Hz, 2 H) 3.08 (s, 4 H) 4.37 (s, 3 H) 5.53 (d, *J*=7.80 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.31 (m, 1 H) 7.38 (m, 3 H) 7.47 (d, *J*=7.19 Hz, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 7.87 (s, 1 H) 8.12 (d, *J*=7.68 Hz, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B108-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (s, 9 H) 2.52 (m, 4 H) 2.68 (m, 4 H) 2.78 (t, 2 H) 2.92 (m, 4 H) 3.07 (m, 4 H) 3.56 (m, 4 H) 4.37 (s, 3 H) 5.16 (m, 1 H) 6.92 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.51 (d, 2 H) 8.34 (s, 1 H) 8.40 (d, 1 H) 9.25 (s, 1 H)
B108-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 9 H) 2.66 (s, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.06 (s, 4 H) 3.75 (s, 3 H) 4.34 (s, 3 H) 4.40 (d, *J*=6.22 Hz, 2 H) 6.82 (ddd, *J*=8.20, 2.59, 0.91 Hz, 1 H) 6.90 (m, 4 H) 7.24 (t, *J*=8.05 Hz, 1 H) 7.53 (d, *J*=8.90 Hz, 2 H) 8.35 (s, 1 H) 8.67 (t, *J*=6.34 Hz, 1 H) 9.25 (s, 1 H)
B19-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (t, 2 H) 3.00 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.34 (s, 3 H) 4.44 (d, 2 H) 6.94 (d, 2 H) 7.34 (m, 5 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (t, 2 H) 2.99 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.34 (s, 3 H) 4.41 (d, 2 H) 6.94 (d, 2 H) 7.15 (m, 2 H) 7.36 (m, 2 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.74 (t, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D24	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (d, 3 H) 2.79 (t, 2 H) 2.96 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (d, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.42 (d, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D47	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.78 (m, 2 H) 2.96 (m, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (m, 2 H) 7.24 (t, 1 H) 7.33 (t, 2 H) 7.41 (m, 2 H) 7.55 (m, 2 H) 8.35 (s, 1 H) 8.42 (s, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D42	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.90 (m, 4 H) 3.05 (m, 4 H) 3.76 (m, 4 H) 4.35 (s, 3 H) 4.40 (m, 2 H) 6.94 (m, 2 H) 7.37 (m, 3 H) 7.55 (m, 2 H) 8.36 (s, 1 H) 8.81 (m, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D41	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (m, 3 H) 1.81 (m, 2 H) 2.78 (m, 4 H) 3.05 (m, 4 H) 3.76 (m, 4 H) 4.36 (s, 3 H) 4.88 (m, 1 H) 6.93 (m, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.55 (m, 2 H) 8.34 (m, 1 H) 8.37 (d, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D68	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (m, 2 H) 2.78 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.36 (s, 3 H) 4.88 (m, 1 H) 6.93 (m, 2 H) 7.33 (m, 5 H) 7.55 (m, 2 H) 8.34 (m, 1 H) 8.40 (m, 1 H) 9.27 (m, 1 H)

B19-X00-M00(C01)-D61	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.96 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (m, 2 H) 7.33 (m, 5 H) 7.55 (m, 2 H) 8.35 (s, 1 H) 8.42 (m, 1 H) 9.27 (m, 1 H)
B19-X00-M00(C01)-D40	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 6.94 (d, 2 H) 7.18 (m, 4 H) 7.55 (d, 2 H) 8.36 (s, 1 H) 8.79 (s, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (t, *J*=7.68 Hz, 2 H) 2.96 (t, *J*=7.74 Hz, 2 H) 3.05 (m, 4 H) 3.74 (m, 6 H) 4.37 (s, 3 H) 5.02 (m, 2 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.56 (d, *J*=9.02 Hz, 2 H) 8.27 (d, *J*=8.29 Hz, 1 H) .35 (s, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.01 (m, 4 H) 3.07 (s, 4 H) 3.77 (m, 4 H) 4.38 (m, 3 H) 4.46 (m, 2 H) 6.95 (m, 1 H) 7.33 (m, 2 H) 7.57 (m, 2 H) 8.38 (s, 1 H) 8.58 (m, 2 H) 8.88 (m, 1 H) 9.31 (s, 1 H)
B19-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.77 (t, *J*=7.80 Hz, 2 H) 2.90 (m, 2 H) 3.06 (m, 4 H) 3.76 (m, 4 H) 4.36 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.20 (m, 1 H) 7.32 (t, *J*=7.68 Hz, 2 H) 7.42 (m, 2 H) 7.56 (d, *J*=9.15 Hz, 2 H) 7.79 (s, 1 H) 8.34 (s, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 5 H) 2.78 (m, 5 H) 3.05 (m, 4 H) 3.56 (m, 4 H) 3.76 (m, 4 H) 4.37 (s, 3 H) 5.17 (m, 1 H) 7.30 (m, 9 H) 8.34 (m, 1 H) 8.40 (m, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 (m, 4 H) 3.06 (m, 4 H) 3.76 (m, 4 H) 4.37 (s, 3 H) 5.54 (m, 1 H) 6.94 (m, 2 H) 7.42 (m, 8 H) 7.86 (m, 1 H) 8.11 (d, 1 H) 8.35 (m, 1 H) 9.28 (m, 1 H)
B19-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 (m, 4 H) 2.52 (s, 6 H) 2.87 (d, 4 H) 3.05 (s, 4 H) 3.76 (s, 4 H) 4.37 (s, 3 H) 5.10 (m, 1 H) 7.30 (m, 9 H) 8.35 (m, 2 H) 9.28 (m, 1 H)
B09-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.82 (t, 2 H) 3.00 (t, 2 H) 3.13 (m, 4 H) 3.75 (s, 3 H) 4.36 (s, 3 H) 4.40 (d, 2 H) 6.59 (m, 1 H) 6.83 (m, 1 H) 6.90 (m, 2 H) 7.14 (m, 1 H) 7.24 (m, 3 H) 8.40 (s, 1 H) 8.67 (t, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.97 (t, 2 H) 3.13 (m, 4 H) 3.73 (m, 2 H) 4.39 (s, 3 H) 5.00 (m, 2 H) 6.59 (m, 1 H) 7.14 (m, 1 H) 7.25 (m, 7 H) 8.26 (d, 1 H) 8.40 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.28 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.14 (m, 4 H) 4.37 (s, 3 H) 6.59 (m, 1 H) 6.71 (m, 1 H) 7.24 (m, 7

	H) 8.40 (s, 1 H) 8.86 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (m, 4 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.83 (m, 10 H) 3.12 (m, 4 H) 4.38 (s, 3 H) 5.10 (m, 1 H) 6.58 (ddd, *J*=8.14, 2.29, 0.67 Hz, 1 H) 7.14 (t, *J*=7.99 Hz, 1 H) 7.24 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.35 (d, *J*=8.66 Hz, 1 H) 8.39 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, *J*=7.80 Hz, 2 H) 2.97 (m, 2 H) 3.14 (m, 4 H) 4.39 (s, 3 H) 5.53 (d, *J*=7.68 Hz, 1 H) 6.58 (dd, *J*=8.11, 2.26 Hz, 1 H) 7.14 (t, *J*=8.05 Hz, 1 H) 7.26 (m, 2 H) 7.31 (m, 1 H) 7.38 (m, 3 H) 7.48 (m, 2 H) 7.87 (s, 1 H) 8.12 (d, *J*=7.68 Hz, 1 H) 8.40 (s, 1 H) 9.34 (s, 1 H)
B09-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.29 (s, 3 H) 2.49 (m, 8 H) 2.80 (t, *J*=7.68 Hz, 3 H) 2.97 (m, 3 H) 3.14 (m, 4 H) 4.39 (s, 3 H) 5.14 (m, 1 H) 6.58 (dd, *J*=8.17, 1.83 Hz, 1 H) 7.15 (t, *J*=8.11 Hz, 1 H) 7.26 (m, 3 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.41 (m, 2 H) 8.36 (s, 1 H) 8.40 (s, 1 H) 9.34 (s, 1 H)
B101-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.83 (t, 2 H) 3.01 (t, 2 H) 3.40 (s, 2 H) 4.36 (s, 3 H) 4.43 (d, 2 H) 7.23 (m, 3 H) 7.34 (m, 3 H) 7.65 (d, 2 H) 8.41 (s, 1 H) 8.71 (t, 1 H) 9.50 (s, 1 H)
B101-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.83 (t, 2 H) 3.00 (t, 2 H) 3.40 (s, 2 H) 4.38 (s, 3 H) 4.44 (d, 2 H) 7.23 (d, 2 H) 7.30 (m, 2 H) 7.65 (d, 2 H) 8.41 (s, 1 H) 8.50 (m, 2 H) 8.87 (t, 1 H) 9.51 (s, 1 H)
B101-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.16 (s, 3 H) 2.34 (m, 8 H) 2.79 (t, 2 H) 2.91 (t, 2 H) 3.40 (s, 2 H) 4.38 (s, 3 H) 7.21 (m, 3 H) 7.32 (m, 2 H) 7.42 (m, 2 H) 7.64 (d, 2 H) 7.80 (s, 1 H) 8.39 (s, 1 H) 9.50 (s, 1 H)
B101-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H) 2.16 (s, 3 H) 2.34 (m, 8 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.41 (m, 2 H) 4.37 (s, 3 H) 5.15 (m, 1 H) 7.15 (dd, 2 H) 7.23 (d, 2 H) 7.46 (dd, 2 H) 7.64 (d, 2 H) 8.40 (s, 1 H) 8.50 (d, 1 H) 9.49 (s, 1 H)
B101-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.40 (s, 2 H) 4.39 (s, 3 H) 5.52 (d, 1 H) 7.23 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 4 H) 7.46 (m, 2 H) 7.64 (d, 2 H) 7.87 (s, 2 H) 8.12 (d, 1 H) 8.40 (s, 1 H) 9.50 (s, 1 H)
B102-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (m, 4 H) 2.83 (t, *J*=7.74 Hz, 2 H) 3.01 (t, *J*=7.68 Hz, 2 H) 3.43 (m, 2 H) 3.59 (m, 4 H) 4.36 (s, 3 H) 4.44 (d, *J*=6.46 Hz, 2 H) 7.25 (m, 3 H) 7.32 (m, 4 H) 7.68 (d, *J*=8.17 Hz, 2 H) 8.41 (s, 1 H) 8.71 (t, *J*=6.28 Hz, 1 H) 9.52 (s, 1 H)
B102-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 10 H)

	2.81 (t, 2 H) 2.95 (t, 2 H) 3.43 (s, 2 H) 3.59 (m, 8 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 7.25 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.66 (d, 2 H) 8.40 (m, 2 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.36 (m, 4 H) 2.79 (t, 2 H) 2.91 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.38 (s, 3 H) 7.25 (m, 3 H) 7.32 (m, 2 H) 7.42 (m, 2 H) 7.66 (d, 2 H) 7.80 (s, 1 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.54 (d, 1 H) 7.25 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.46 (m, 2 H) 7.66 (d, 2 H) 7.87 (s, 2 H) 8.12 (d, 1 H) 8.41 (s, 1 H) 9.52 (s, 1 H)
B102-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (m, 4 H) 2.37 (m, 4 H) 2.82 (t, 2 H) 2.97 (t, 2 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 4.37 (s, 3 H) 7.16 (m, 1 H) 7.24 (m, 6 H) 7.66 (d, 2 H) 8.40 (s, 1 H) 8.87 (s, 1 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (m, 4 H) 2.36 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.35 (m, 6 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.11 (m, 1 H) 7.25 (m, 3 H) 7.35 (m, 2 H) 7.43 (m, 2 H) 7.66 (d, 2 H) 8.40 (m, 2 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.38 (m, 10 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.11 (m, 1 H) 7.25 (m, 3 H) 7.33 (m, 2 H) 7.40 (m, 2 H) 7.66 (d, 2 H) 8.35 (d, 1 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B105-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.92 (m, 4 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 3.75 (s, 3 H) 4.39 (m, 5 H) 6.90 (m, 4 H) 7.25 (m, 2 H) 7.57 (m, 1 H) 7.77 (m, 1 H) 8.42 (m, 1 H) 8.68 (s, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.90 (m, 4 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 4.42 (s, 3 H) 5.53 (m, 1 H) 6.93 (m, 1 H) 7.47 (m, 8 H) 7.82 (m, *J*=39.51 Hz, 2 H) 8.12 (m, 1 H) 8.42 (m, 1 H) 9.55 (m, 1 H)
B105-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 (m, 4 H) 2.38 (m, 4 H) 2.90 (m, 4 H) 3.45 (m, 4 H) 3.59 (m, 4 H) 4.42 (s, 3 H) 6.93 (m, 1 H) 7.25 (m, 7 H) 7.57 (m, 1 H) 7.76 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.90 (m, 4 H) 3.45 (m, 2 H) 3.60 (m, 4 H) 3.73 (m, 2 H) 4.42 (m, 3 H) 5.00 (m, 2 H) 6.92 (m, 1 H) 7.32 (m, 6 H) 7.57 (m, 1 H) 7.77 (m, 1 H) 8.27 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.38 (m, 4 H) 2.98 (m, 4 H) 3.44 (m, 2 H) 3.60 (m, 4 H) 4.40 (s, 3 H) 6.92 (m, 1 H) 7.20 (m, 6 H) 7.58 (m, 1 H) 7.77 (s, 1 H) 8.42 (s, 1 H) 9.20 (m, 2 H)

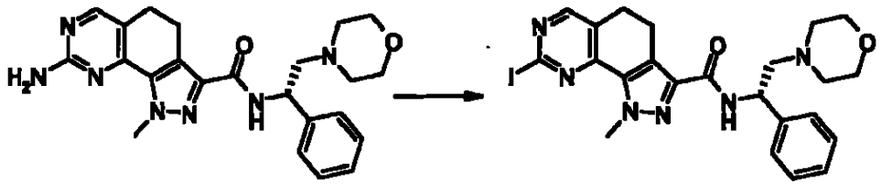
B105-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.52 (m, 8 H) 2.81 (m, 4 H) 3.45 (m, 2 H) 3.60 (s, 4 H) 4.42 (s, 3 H) 5.11 (m, 1 H) 6.92 (m, 1 H) 7.25 (m, 6 H) 7.57 (m, 1 H) 7.76 (m, 1 H) 8.34 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B104-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (s, 6 H) 2.21 (s, 3 H) 2.40 (m, 8 H) 2.80 (t, 2 H) 2.92 (t, 2 H) 3.44 (s, 2 H) 4.40 (s, 3 H) 6.91 (m, 1 H) 7.32 (m, 4 H) 7.42 (m, 2 H) 7.55 (m, 1 H) 7.75 (m, 1 H) 7.81 (m, 1 H) 8.41 (s, 1 H) 9.53 (s, 1 H)
B104-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.20 (m, 3 H) 2.40 (m, 8 H) 2.82 (t, 2 H) 2.98 (t, 2 H) 3.44 (s, 2 H) 4.39 (s, 3 H) 6.90 (m, 1 H) 7.25 (m, 6 H) 7.56 (m, 1 H) 7.76 (m, 1 H) 8.42 (s, 1 H) 8.87 (s, 1 H) 9.53 (s, 1 H)
B104-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.42 (m, 8 H) 2.82 (t, 2 H) 2.97 (t, 2 H) 3.44 (s, 2 H) 4.41 (s, 3 H) 5.53 (d, 1 H) 6.91 (d, 1 H) 7.24 (m, 1 H) 7.38 (m, 3 H) 7.46 (m, 2 H) 7.56 (m, 1 H) 7.75 (m, 1 H) 7.87 (s, 2 H) 8.12 (m, 1 H) 8.42 (s, 1 H) 9.54 (s, 1 H)
B104-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 2.39 (m, 8 H) 2.83 (t, 2 H) 3.01 (t, 2 H) 3.43 (s, 2 H) 3.75 (s, 3 H) 4.38 (s, 3 H) 4.41 (d, 2 H) 6.83 (m, 1 H) 6.90 (m, 3 H) 7.24 (m, 2 H) 7.56 (m, 1 H) 7.76 (m, 1 H) 8.42 (s, 1 H) 8.68 (t, 1 H) 9.53 (s, 1 H)
B103-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 (m, 1 H) 1.95 (m, 1 H) 2.09 (m, 1 H) 2.26 (m, 1 H) 2.82 (m, 5 H) 3.00 (t, 2 H) 3.34 (m, 4 H) 4.34 (s, 3 H) 4.43 (d, 2 H) 4.65 (m, 1 H) 7.02 (m, 2 H) 7.25 (m, 1 H) 7.33 (m, 4 H) 7.62 (m, 2 H) 8.38 (s, 1 H) 8.67 (t, 1 H) 9.39 (s, 1 H)
B103-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 1.79 (m, 2 H) 2.00 (m, 2 H) 2.56 (s, 3 H) 2.68 (m, 2 H) 2.78 (t, 2 H) 2.90 (t, 2 H) 2.99 (m, 2 H) 4.35 (s, 3 H) 4.42 (m, 1 H) 6.97 (d, 2 H) 7.21 (m, 1 H) 7.32 (m, 2 H) 7.41 (m, 2 H) 7.58 (d, 2 H) 7.78 (s, 1 H) 8.35 (s, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 (d, 3 H) 1.84 (m, 2 H) 2.01 (m, 2 H) 2.79 (m, 4 H) 2.96 (m, 4 H) 4.34 (s, 3 H) 4.43 (m, 1 H) 5.15 (m, 1 H) 6.97 (d, 2 H) 7.15 (m, 2 H) 7.46 (m, 2 H) 7.58 (d, 2 H) 8.36 (s, 1 H) 8.47 (d, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (m, 2 H) 1.96 (m, 2 H) 2.34 (s, 3 H) 2.42 (m, 2 H) 2.79 (m, 6 H) 4.36 (m, 4 H) 5.52 (d, 1 H) 6.94 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.46 (m, 2 H) 7.56 (d, 2 H) 7.87 (s, 2 H) 8.11 (d, 1 H) 8.36 (s, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 (m, 2 H) 1.94 (m, 2 H) 2.32 (s, 3 H) 2.39 (m, 2 H) 2.80 (m, 4 H) 2.99 (t, 2 H) 4.35 (m, 4 H) 4.44 (d, 2 H) 6.94 (d, 2 H) 7.31 (m, 2

	H) 7.57 (d, 2 H) 8.37 (s, 1 H) 8.50 (m, 2 H) 8.85 (t, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 (m, 4 H) 2.20 (m, 3 H) 2.37 (m, 4 H) 2.55 (m, 4 H) 2.88 (m, *J*=59.63 Hz, 6 H) 4.28 (m, 1 H) 4.35 (s, 3 H) 5.10 (m, 1 H) 5.35 (none, 1 H) 6.93 (m, 2 H) 7.31 (m, 5 H) 7.56 (m, 2 H) 8.35 (m, 2 H) 9.32 (m, 6 H)
B103-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (s, 4 H) 1.91 (m, 4 H) 2.20 (m, 3 H) 2.52 (m, 8 H) 2.87 (m, *J*=66.33 Hz, 4 H) 3.04 (m, 2 H) 4.28 (m, 1 H) 4.35 (s, 3 H) 5.08 (m, 1 H) 6.93 (m, 2 H) 7.38 (m, 7 H) 8.35 (m, 2 H) 9.32 (m, 1 H)
B103-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.78 (m, *J*=106.57 Hz, 4 H) 2.41 (m, 7 H) 2.87 (m, *J*=68.16 Hz, 4 H) 3.73 (m, 2 H) 4.28 (m, 1 H) 4.36 (s, 3 H) 5.00 (m, 2 H) 6.93 (m, 2 H) 7.32 (m, 5 H) 7.56 (m, 2 H) 8.26 (m, 1 H) 8.36 (m, 1 H) 9.32 (m, 1 H)
B103-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (m, 4 H) 1.79 (m, *J*=107.43 Hz, 4 H) 2.43 (m, 7 H) 2.88 (m, *J*=66.33 Hz, 4 H) 4.29 (m, 1 H) 4.34 (m, 3 H) 6.93 (m, 2 H) 7.22 (m, 5 H) 7.56 (m, 2 H) 8.36 (s, 1 H) 8.86 (m, 1 H) 9.32 (m, 1 H)
B00-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.71 (t, 2 H) 2.90 (t, 2 H) 3.57 (m, 4 H) 4.36 (m, 3 H) 5.15 (m, 1 H) 6.55 (s, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 8.17 (s, 1 H) 8.36 (d, 1 H).
B00-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 (t, 2 H) 2.94 (t, 2 H) 4.35 (s, 3 H) 4.43 (d, 2 H) 6.56 (s, 2 H) 7.31 (m, 2 H) 8.18 (s, 1 H) 8.50 (m, 2 H) 8.82 (t, 1 H).
B113-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (t, 2 H) 3.00 (t, 2 H) 4.35 (s, 3 H) 4.44 (d, 2 H) 7.16 (m, 2 H) 7.30 (m, 2 H) 7.71 (m, 2 H) 8.41 (s, 1 H) 8.50 (m, 2 H) 8.87 (t, 1 H) 9.55 (s, 1 H)
B112-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (t, *J*=7.68 Hz, 2 H) 3.01 (t, *J*=7.68 Hz, 2 H) 4.35 (s, 3 H) 4.44 (d, *J*=6.34 Hz, 2 H) 7.26 (m, 5 H) 7.36 (d, *J*=9.02 Hz, 2 H) 7.76 (d, *J*=9.02 Hz, 2 H) 8.44 (s, 1 H) 8.72 (t, *J*=6.40 Hz, 1 H) 9.68 (s, 1 H)
B04-X04-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 (t, 2 H) 2.99 (t, 2 H) 3.71 (s, 3 H) 7.25 (m, 1 H) 7.44 (s, 1 H) 7.51 (m, 3 H) 7.66 (m, 2 H) 8.55 (s, 1 H)
B10-X00-M04(C15)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 6 H) 3.05 (m, 4 H) 3.33 (m, 5 H) 6.28 (s, 2 H) 6.80 (d, 2 H) 7.33 (s, 2 H) 7.47 (m, 7 H) 7.63 (d, 2 H) 7.66 (s, 1 H) 8.42 (s, 1 H) 9.34 (s, 1 H)
B09-X00-M04(C03)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (m, 9 H) 1.64 (t, 2 H) 2.86 (m, 15 H) 4.84 (t, 2 H) 6.67 (m, 1 H) 7.21

	(m, 3 H) 7.39 (s, 2 H) 8.41 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C14)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, 3 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.61 (q, 2 H) 2.84 (t, 2 H) 3.03 (m, 6 H) 6.16 (s, 2 H) 6.75 (d, 2 H) 6.83 (s, 1 H) 7.29 (br. s, 2 H) 7.36 (d, 2 H) 7.45 (br. s, 1 H) 8.38 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C14)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H) 2.24 (s, 3 H) 2.46 (m, 4 H) 2.60 (q, 2 H) 2.85 (t, 2 H) 3.02 (m, 6 H) 4.41 (d, 2 H) 6.18 (s, 2 H) 6.74 (d, 2 H) 6.83 (s, 1 H) 7.23 (m, 1 H) 7.31 (m, 4 H) 7.37 (d, 2 H) 8.38 (s, 1 H) 8.69 (t, 1 H) 9.26 (s, 1 H)
B08-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 2.96 (m, 2 H) 3.83 (s, 3 H) 4.23 (s, 3 H) 6.96 (m, 3 H) 7.22 (s, 1 H) 7.43 (s, 1 H) 8.00 (m, 1 H) 8.11 (s, 1 H) 8.35 (s, 1 H)
B36-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (t, 2 H) 2.95 (t, 2 H) 4.28 (s, 3 H) 5.95 (s, 2 H) 6.84 (d, 1 H) 7.06 (dd, 1 H) 7.22 (s, 1 H) 7.34 (d, 1 H) 7.42 (s, 1 H) 8.34 (s, 1 H) 9.34 (s, 1 H)

Example 52

8-Iodo-1-methyl-N-[(1S)-2-morpholin-4-yl-1-phenylethyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide

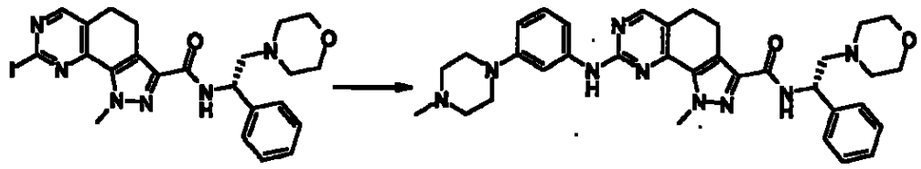


To a well stirred and warm suspension of 8-amino-1-methyl-N-[(1S)-2-morpholin-4-yl-1-phenylethyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (3 g, 6.92 mmol) in dimethoxyethane (240 mL), maintained in an inert atmosphere of argon, cesium iodide (2.16 g, 8.3 mmol), bisublimated iodine (870 mg, 3.46 mmol), copper iodide (460 mg, 2.42 mmol) and isopentyl nitrite (1.71 mL, 1.5 g, 12.46 mmol) were added, in sequence. The reaction mixture was stirred vigorously at 65-70°C for 18 hours. After cooling in an ice-water bath, the solid was filtered off and the filtrate was diluted with dichloromethane (100 mL), washed with 30% ammonium hydroxide (50 mL), sodium thiosulphate (100 mL), brine and dried over anhydrous Na_2SO_4. The crude was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 95:59) and 1.48 g of the title compound was isolated (40% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.89 (t, 2 H) 2.99 (t, 2 H) 4.30 (s, 3 H) 5.17 (m, 1 H) 7.22 (m, 1 H) 7.34 (m, 2 H) 7.41 (m, 2 H) 8.47 (s, 1 H)

Example 53

1-methyl-8-{[3-(4-methylpiperazin-1-yl)phenyl]amino}-N-[(1S)-2-morpholin-4-yl-1-phenylethyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B09-X00-M00(C01)-D38]



Palladium acetate [$Pd(OAc)_2$] (10 mg, 0.022 mmol, 10%), (±)-BINAP (14 mg, 0.022 mmol, 10%) and dimethylformamide (4 mL) were charged in a round-bottom flask flushed with argon. The mixture was stirred under argon for 30 minutes. Then, 3-(4-methylpiperazin-1-yl)phenylamine (84 mg, 0.44 mmol), 8-iodo-1-methyl-N-[(1S)-2-morpholin-4-yl-1-phenylethyl]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (120 mg, 0.22 mmol), potassium carbonate (670 mg, 4.85 mmol) and dimethylformamide (1.5 mL) were added. The resulting mixture was heated at 80°C in an oil bath under argon with good stirring for 1.5 hours.

After cooling to room temperature, the reaction mixture was poured into water and extracted with dichloromethane. The organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuo, the crude was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 95:5) to afford 40 mg (30% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 8 H) 2.80 (t, 2 H) 2.94 (m, 4 H) 3.13 (m, 4 H) 3.56 (m, 4 H) 4.39 (s, 3 H) 5.16 (m, 1 H) 6.59 (m, 1 H) 7.14 (m, 1 H) 7.24 (m, 2 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.39 (m, 2 H) 9.33 (s, 1 H).

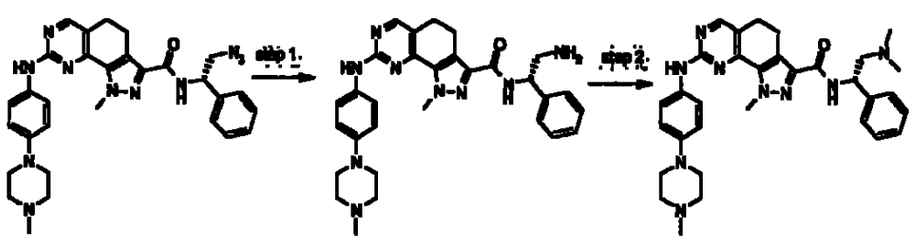
By working analogously the following compounds were prepared:

Table XIV

B107-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.80 (t, 2 H) 2.97 (m, 2 H) 3.09 (m, 4 H) 3.57 (m, 4 H) 3.76 (m, 4 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 6.60 (m, 1 H) 7.16 (m, 1 H) 7.42 (m, 6 H) 8.40 (m, 2 H) 9.35 (s, 1 H)
B105-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 10 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.34 (m, 10 H) 4.41 (s, 3 H)

	5.17 (m, 1 H) 6.93 (m, 1 H) 7.34 (m, 4 H) 7.42 (m, 2 H) 7.58 (m, 1 H) 7.77 (m, 1 H) 8.41 (m, 2 H) 9.54 (s, 1 H)
B103-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 (m, 2 H) 1.92 (m, 2 H) 2.21 (m, 5 H) 2.52 (m, 4 H) 2.65 (m, 2 H) 2.79 (t, 2 H) 2.95 (m, 4 H) 3.56 (m, 4 H) 4.29 (m, 1 H) 4.36 (s, 3 H) 5.17 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.56 (d, 2 H) 8.35 (s, 1 H) 8.40 (d, 1 H) 9.32 (s, 1 H)
B101-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 2.52 (m, 8 H) 2.80 (t, 2 H) 2.95 (m, 4 H) 3.33 (m, 6 H) 3.56 (m, 4 H) 4.39 (s, 3 H) 5.17 (m, 1 H) 7.23 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.65 (d, 2 H) 8.40 (m, 2 H) 9.50 (s, 1 H)
B104-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H) 2.42 (m, 13 H) 2.81 (t, *J*=7.80 Hz, 2 H) 2.95 (m, 3 H) 3.44 (s, 2 H) 3.57 (m, 4 H) 4.41 (s, 3 H) 5.17 (m, 1 H) 6.90 (d, *J*=7.56 Hz, 1 H) 7.24 (t, *J*=7.68 Hz, 2 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.43 (m, 2 H) 7.57 (dd, *J*=8.29, 0.98 Hz, 1 H) 7.76 (t, *J*=1.95 Hz, 1 H) 8.41 (d, *J*=7.68 Hz, 1 H) 8.41 (s, 1 H) 9.53 (s, 1 H)
B110-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (m, 6 H) 2.73 (m, 16 H) 3.57 (m, 4 H) 4.39 (s, 3 H) 5.17 (m, 1 H) 7.26 (m, 2 H) 7.25 (m, 1 H) 7.33 (t, *J*=7.56 Hz, 2 H) 7.43 (m, 2 H) 7.70 (s, 2 H) 8.42 (m, 2 H) 9.55 (s, 1 H)
B106-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 (m, 2 H) 1.98 (m, 2 H) 2.52 (m, 7 H) 2.81 (m, 8 H) 3.56 (m, 4 H) 4.41 (m, 4 H) 5.17 (m, 1 H) 6.60 (m, 1 H) 7.26 (m, 5 H) 7.44 (m, 3 H) 8.42 (m, 2 H) 9.50 (s, 1 H)
B111-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J*=7.19 Hz, 3 H) 2.46 (m, 5 H) 2.80 (t, *J*=7.74 Hz, 2 H) 2.93 (m, 3 H) 3.56 (q, 4 H) 4.03 (q, *J*=7.19 Hz, 2 H) 4.20 (s, 3 H) 5.16 (m, 1 H) 6.20 (d, *J*=1.71 Hz, 1 H) 7.24 (t, *J*=7.32 Hz, 1 H) 7.33 (t, *J*=7.44 Hz, 2 H) 7.42 (m, 3 H) 8.36 (s, 1 H) 8.41 (d, *J*=6.95 Hz, 1 H) 9.23 (s, 1 H)

Example 54



Step 1. N-[(1S)-2-amino-1-phenylethyl]-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B10-X00-M00(C01)-D71]

To a solution of 129 mg (0.228 mmol) of N-[(1S)-2-azido-1-phenylethyl]-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide in 16 mL of methanol, 65 mg (1.2 mmol) of NH_4Cl dissolved in 3.2 mL of water and 39 mg of iron (0.7 mmol) were added and the mixture refluxed overnight. The suspension was cooled to room temperature and filtered. After removal of methanol, solid Na_2CO_3 was added portionwise to the aqueous phase up to pH 10 and the product was then extracted with dichloromethane. Flash chromatography of the crude (eluant dichloromethane/methanol 95/5) yielded 94 mg of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.47 (m, 4 H) 2.78 (t, *J*=7.68 Hz, 2 H) 2.96 (m, 3 H) 3.08 (m, 5 H) 4.37 (s, 3 H) 5.01 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.31 (m, 5 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.54 (d, *J*=8.17 Hz, 1 H) 9.26 (s, 1 H).

By working according to the above method the following compound was prepared:

B10-X00-M03(C01)-D71

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 3 H) 1.34 (s, 3 H) 2.24 (s, 3 H) 2.45 - 2.49 (m, 4 H) 2.62 - 2.72 (m, 2 H) 2.90 - 3.05 (m, 2 H) 3.06 - 3.10 (m, 4 H) 4.35 (s, 3 H) 5.01 (td, *J*=8.20, 5.67 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.24 - 7.29 (m, 1 H) 7.33 - 7.38 (m, 2 H) 7.38 - 7.41 (m, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.65 (d, *J*=8.29 Hz, 1 H) 9.26 (s, 1 H).

Step 2. N-[(1S)-2-(dimethylamino)-1-phenylethyl]-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B10-X00-M00(C01)-D72]

To a solution of 50 mg (0.091 mmol) of N-[(1S)-2-amino-1-phenylethyl]-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide in methanol (5 mL), 0.027 mL of formaldehyde (40 % aqueous solution 0.364 mmol) and acetic acid (0.02 mL) were added. After 30 minutes, 77 mg (0.364 mmol) of sodiumtriacetoxyborohydride were added and the mixture was stirred for 5 hours. The solvent was removed under vacuo, the crude was dissolved in

water and Na_2CO_3 was added portionwise up to basic pH. The product was extracted with dichloromethane as the sole compound (34 mg, 66 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 9 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.11 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.53 (d, 2 H) 8.34 (m, 2 H) 9.26 (s, 1 H).

By working analogously the following compounds were prepared:

1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-N-{(1S)-2-[(1-methylpiperidin-4-yl)amino]-1-phenylethyl}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B10-X00-M00(C01)-D145]

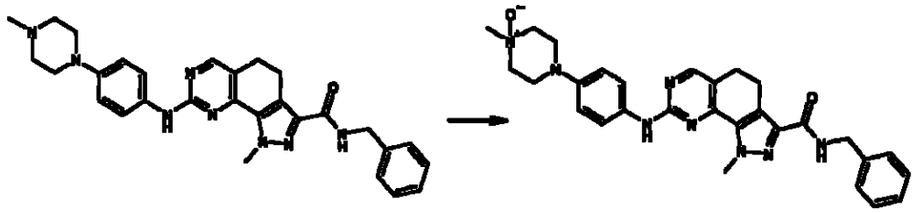
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.76 (m, 4 H) 2.73 (m, 24 H) 4.39 (s, 3 H) 5.34 (m, 1 H) 6.98 (d, 2 H) 7.30 (m, 1 H) 7.38 (m, 2 H) 7.43 (m, 2 H) 7.57 (d, 2 H) 8.36 (s, 1 H) 8.75 (s, 1 H) 9.33 (bs, 1 H)

B10-X00-M03(C01)-D72

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 3 H) 1.32 (s, 3 H) 2.24 (s, 6 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.67 (m, 2 H) 2.80 (m, 2 H) 3.08 (m, 4 H) 4.34 (s, 3 H) 5.12 (td, *J*=8.20, 5.67 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.25 (m, 1 H) 7.34 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.33 (s, 1 H) 8.45 (d, *J*=8.29 Hz, 1 H) 9.26 (s, 1 H)

Example 55

N-benzyl-1-methyl-8-{[4-(4-methyl-4-oxidopiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide

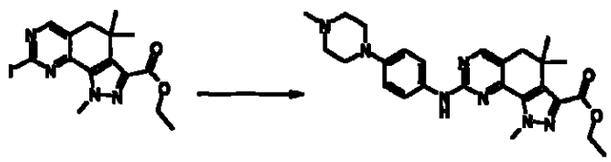


To a solution of 39.4 mg (0.0774 mmol) of N-benzyl-1-methyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide, 17.4 mg (0.0774 mg) of 3-chlorobenzenecarboperoxoic acid were added and the mixture was stirred at room temperature. After 45 minutes an aqueous solution of $NaHCO_3$ was added and the solvent removed. Treatment with methanol and filtration afforded 26.6 mg of the title compound (66 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (t, *J*=7.74 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.37 (m, 8 H) 3.15 (s, 3 H) 4.34 (s, 3 H) 4.43 (d, *J*=6.34 Hz, 2 H) 6.98 (d, *J*=9.15 Hz, 2 H) 7.24 (m, 1 H) 7.33 (m, 4 H) 7.57 (d, *J*=9.15 Hz, 2 H) 8.36 (s, 1 H) 8.70 (t, *J*=6.34 Hz, 1 H) 9.30 (s, 1 H).

Example 56

Ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1 H- pyrazolo[4,3-h]quinazoline-3-carboxylate [B10-X00-M03(C01)-D01]



$Pd(OAc)_2$ (762.34 mg, 3.395 mmol), (±)-BINAP (2.145 g, 3.395 mmol) and dimethylformamide (250 mL) were charged in a round-bottom flask flushed with argon. The mixture was stirred under argon for 30 minutes. Then 4-(4-methyl-piperazin-1-yl)-phenylamine (19.493 g, 101.908 mmol), ethyl 8-iodo-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (14.00 g, 33.961 mmol), K_2CO_3 (60.00 g, 434.112 mmol) and dimethylformamide (250 mL) were added. The resulting mixture was stirred at room temperature for 1 hour and then heated to 80°C in an oil bath under argon with good stirring for 3 hours.

After cooling to room temperature, the reaction mixture was filtered by suction filtration washing with dichloromethane and the filtrate was evaporated to dryness. The crude was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 94:6) to afford 11.60 g (yield 72%) of pure title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.71 (s, 2 H) 3.03 - 3.15 (m, 4 H) 4.32 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 9.28 (s, 1 H).

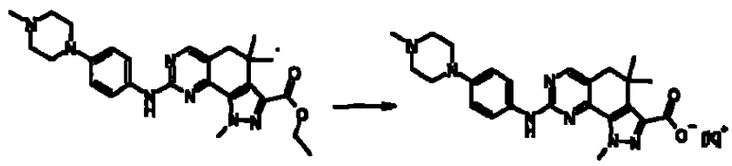
By working according to the above method the following compound was prepared:

Table XV

B19-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.71 (s, 2 H) 3.01 - 3.08 (m, 4 H) 3.70 - 3.80 (m, 4 H) 4.32 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 9.30 (s, 1 H)

Example 57

8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid potassium salt [B10-X00-M03(C01)-D02]



To a suspension of ethyl 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (11.60 g, 24.390 mmol) in anhydrous ethanol (450 mL), 1.5 M potassium hydroxide in 95% ethanol (63 mL) was added under good stirring and the mixture was heated to reflux for 3 hours. After cooling in an ice bath, a solid was formed, that was filtered washing with ethanol, dried at 40°C under vacuum to yield 11.8 g (quantitative yield) of white solid title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.58 (s, 2 H) 3.03 - 3.15 (m, 4 H) 4.17 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.24 (s, 1 H) 9.12 (s, 1 H)

By working according to the above method the following compounds were prepared:

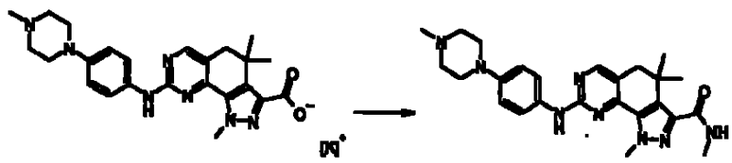
Table XVI

B04-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.73 (s, 2 H) 4.34 (s, 3 H) 6.98 (tt, *J* 7.36, 1.13, 1.10 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.38 Hz, 2 H) 7.71 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.42 (s, 1 H) 9.53 (s, 1 H) 12.84 (s, 1 H)
B12-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.24 (s, 3 H) 2.45 (s, 4 H) 2.61 (s, 2 H) 2.84 (t, *J* 4.51 Hz, 4 H) 4.18 (s, 3 H) 7.52 (d, *J* 9.02 Hz, 1 H) 7.94 (dd, *J* 8.90, 2.44 Hz, 1 H) 8.09 (d, *J* 2.56 Hz, 1 H) 8.34 (s, 1 H) 9.63 (s, 1 H)
B13-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.61 (s, 2 H) 2.94 (t, *J* 4.51 Hz, 4 H) 4.20 (s, 3 H) 7.12 (d, *J* 8.90 Hz, 1 H) 7.53 (dd, *J* 8.78, 2.56 Hz, 1 H) 7.99 (d, *J* 2.56 Hz, 1 H) 8.31 (s, 1 H) 9.45 (s, 1 H)
B00-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.51 (s, 2 H) 4.16 (s, 3 H) 6.37 (s, 2 H) 8.07 (s, 1 H)
B19-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.58 (s, 2 H) 3.01 – 3.09 (m, 4 H) 3.71 – 3.79 (m, 4 H) 4.18 (s, 3 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.57 (d, *J*=9.15

	Hz, 2 H) 8.25 (s, 1 H) 9.14 (s, 1 H)
B109-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.48 (m, 4 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.96 (m, 6 H) 4.27 (s, 3 H) 6.99 (dd, *J*=10.00, 8.90 Hz, 1 H) 7.38 (ddd, *J*=8.87, 2.47, 0.85 Hz, 1 H) 7.68 (dd, *J*=15.49, 2.44 Hz, 1 H) 8.34 (s, 1 H) 9.45 (s, 1 H)
B13-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (s, 6 H) 2.25 (s, 3 H) 2.51 (m, 4 H) 2.91 (s, 2 H) 2.94 (t, *J* 4.39 Hz, 4 H) 4.25 (s, 3 H) 7.13 (d, *J* 8.78 Hz, 1 H) 7.53 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.00 (d, *J* 2.44 Hz, 1 H) 8.43 (s, 1 H) 9.49 (s, 1 H)
B12-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (s, 6 H) 2.24 (s, 3 H) 2.45 (s, 4 H) 2.84 (t, *J* 4.63 Hz, 4 H) 2.91 (s, 2 H) 4.23 (s, 3 H) 7.52 (d, *J* 8.78 Hz, 1 H) 7.93 (dd, *J* 8.78, 2.32 Hz, 1 H) 8.11 (d, *J* 2.56 Hz, 1 H) 8.44 (s, 1 H) 9.67 (s, 1 H)
B04-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.92 (s, 2 H) 4.37 (s, 3 H) 6.98 (tt, *J* 7.33, 1.10, 1.07 Hz, 1 H) 7.32 (dd, *J* 8.41, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.52 (s, 1 H) 9.56 (s, 1 H) 12.80 (s, 1 H)
B10-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.89 (s, 2 H) 3.07 (m, 4 H) 4.21 (s, 3 H) 6.89 (d, *J*=9.17 Hz, 2 H) 7.54 (d, *J*=9.17 Hz, 2 H) 8.35 (s, 1 H) 9.14 (s, 1 H)

Example 58

8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B10-X00-M03(C01)-D04]



To a suspension of 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid potassium salt (9.5 g, 19.561 mmol) in a 1:1 mixture of anhydrous tetrahydrofurane and dimethylformamide (50 mL), 2M methylamine in tetrahydrofurane (21.12 mL, 42.24 mmol), 1-hydroxybenzotriazole (5.332 g, 39.458 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (7.567 g, 39.473 mmol) were added in that order, and the reaction mixture stirred at room temperature for 18 hours.

The reaction mixture was poured into water (2.5 L) and extracted with dichloromethane (4 x 250 mL). The combined organic extracts were washed with water, essicated over anhydrous sodium sulphate, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography on silica gel (eluant: methylene chloride/methanol 94:6) to afford 8.20 g (yield 92%) of pure title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.26 (s, 3 H) 2.44 – 2.54 (m, 4 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.04 – 3.13 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.84 Hz, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)

By working according to the above method the following compounds were prepared:

Table XVII

B19-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.02 – 3.09 (m, 4 H) 3.72 – 3.79 (m, 4 H) 4.31 (s, 3 H) 6.93 (d, *J*=9.02 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)
B10-X00-M03(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.28 (s, 3 H) 2.50 – 2.57 (m, 4 H) 2.70 (s, 2 H) 3.04 – 3.13 (m, 4 H) 4.26 (d, *J*=5.85 Hz, 2 H) 4.34 (s, 3 H) 6.92 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 8.94 (t, *J*=5.85 Hz, 1 H) 9.28 (s, 1 H)
B10-X00-M03(C01)-D30	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.28 (s, 3 H) 2.47 – 2.59 (m, 4 H) 2.69 (s, 2 H) 3.02 – 3.16 (m, 4 H) 3.83 (d, *J*=5.73 Hz, 2 H) 4.34 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.08 (s, 1 H) 7.36 (s, 1 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.12 (t, *J*=5.67 Hz, 1 H) 8.35 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M03(C01)-D162 tri hydrochloride salt	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.70 (s, 2 H) 2.85 (d, *J*=4.63 Hz, 3 H) 2.95 – 3.05 (m, 2 H) 3.11 – 3.25 (m, 2 H) 3.52 (d, *J*=11.46 Hz, 2 H) 3.67 (s, 3 H) 3.74 (d, *J*=13.66 Hz, 2 H) 4.00 (d, *J*=5.97 Hz, 2 H) 4.34 (s, 3 H) 6.99 (d, *J*=9.15 Hz, 2 H) 7.60 (d, *J*=9.02 Hz, 2 H) 8.37 (s, 1 H) 8.54 (t, *J*=6.04 Hz, 1 H) 9.39 (s, 1 H) 10.23 (s, 1 H)
B10-X00-M03(C01)-D20	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 6 H) 2.27 (s, 3 H) 2.50 – 2.57 (m, 4 H) 2.71 (s, 2 H) 3.07 – 3.13 (m, 4 H) 4.38 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.06 – 7.15 (m, 1 H) 7.31 – 7.40 (m, 2 H) 7.55 (d, *J*=9.15 Hz, 2 H) 7.80 (dd, *J*=8.54, 0.98 Hz, 2 H) 8.37 (s, 1 H) 9.29 (s, 1 H) 10.29 (s, 1 H)
B10-X00-M03(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.70 (s, 2 H) 2.84 (d, *J*=4.15 Hz, 3 H) 3.03 (t, *J*=12.56 Hz, 2 H) 3.10 – 3.25 (m, 2 H) 3.36 – 3.55 (m, 2 H)

	3.74 (d, *J*=13.05 Hz, 2 H) 4.32 (s, 3 H) 4.45 (d, *J*=6.34 Hz, 2 H) 7.00 (d, *J*=9.02 Hz, 2 H) 7.21 – 7.29 (m, 1 H) 7.31 – 7.36 (m, 4 H) 7.59 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 8.77 (t, *J*=6.34 Hz, 1 H) 9.46 (s, 1 H) 10.46 (s, 1 H)
B10-X00-M03(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (s, 3 H) 1.33 (s, 3 H) 2.27 (s, 3 H) 2.48 – 2.56 (m, 4 H) 2.67 (s, 2 H) 3.04 – 3.14 (m, 4 H) 3.71 (t, *J*=6.04 Hz, 2 H) 4.35 (s, 3 H) 4.96 (t, *J*=5.61 Hz, 1 H) 5.02 (dt, *J*=7.83, 6.20 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.22 – 7.28 (m, 1 H) 7.34 (t, *J*=7.44 Hz, 2 H) 7.38 – 7.42 (m, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.42 (d, *J*=8.17 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M03(C01)-D70	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (s, 3 H) 1.36 (s, 3 H) 2.27 (s, 3 H) 2.45 - 2.54 (m, 4 H) 2.61 - 2.72 (m, 2 H) 3.07 - 3.12 (m, 4 H) 3.61 - 3.68 (m, *J*=12.44, 5.12 Hz, 1 H) 3.80 (dd, *J*=12.44, 9.51 Hz, 1 H) 4.35 (s, 3 H) 5.27 (td, *J*=9.21, 5.00 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.27 - 7.33 (m, 1 H) 7.38 (t, *J*=7.44 Hz, 2 H) 7.48 (d, *J*=7.07 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.93 (d, *J*=9.02 Hz, 1 H) 9.27 (s, 1 H)
B10-X00-M03(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (d, *J*=6.54 Hz, 3 H) 1.31 (s, 6 H) 2.17 (s, 6 H) 2.22 (s, 3 H) 2.45 (m, 6 H) 2.65 (s, 2 H) 3.04 (m, 4 H) 4.04 (m, 1 H) 4.29 (s, 3 H) 6.90 (d, *J*=9.02 Hz, 2 H) 7.49 (d, *J*=9.02 Hz, 2 H) 7.91 (d, *J*=8.46 Hz, 1 H) 8.32 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M02(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.26 (s, 3 H) 2.47 (m, 4 H) 2.93 (s, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.32 Hz, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.53 (d, *J*=9.32 Hz, 2 H) 8.44 (s, 1 H) 9.28 (s, 1 H)

Reported below are the analytical HPLC/Mass data for some representative compounds of the invention.

Table XVIII

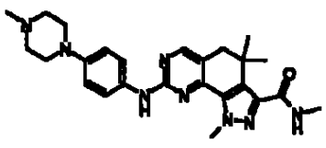
	M+H	Time 1	Method
B10-X00-M03(C01)-D136	560.34	2.2	1
B10-X00-M03(C01)-D26	532.34	2.25	1
B10-X00-M03(C01)-D66	518.33	2.43	1
B10-X00-M03(C01)-D137	534.32	2.34	1
B10-X00-M03(C01)-D116	558.36	2.45	1
B10-X00-M03(C01)-D79	535.31	2.5	1
B10-X00-M03(C01)-D123	517.3	2.57	1
B10-X00-M03(C01)-D135	517.3	2.64	1
B10-X00-M03(C01)-D138	505.3	2.63	1
B10-X00-M03(C01)-D139	506.29	2.46	1

B10-X00-M03(C01)-D95	521.29	2.77	1
B10-X00-M03(C01)-D119	521.29	2.77	1
B10-X00-M03(C01)-D81	558.36	2.6	1
B10-X00-M03(C01)-D115	544.34	2.45	1
B10-X00-M03(C01)-D105	531.31	2.9	1
B10-X00-M03(C01)-D140	545.33	2.87	1
B10-X00-M03(C01)-D100	545.33	3.05	1
B10-X00-M03(C01)-D82	505.3	3.1	1
B10-X00-M03(C01)-D97	505.3	3.19	1
B10-X00-M03(C01)-D121	572.34	3.23	1
B10-X00-M03(C01)-D06	491.26	2.93	1
B10-X00-M03(C01)-D104	505.3	3.21	1
B10-X00-M03(C01)-D113	531.31	3.07	1
B10-X00-M03(C01)-D83	549.29	3.45	1
B10-X00-M03(C01)-D131	519.31	3.47	1
B10-X00-M03(C01)-D102	475.29	3.54	1
B10-X00-M03(C01)-D122	545.33	3.32	1
B10-X00-M03(C01)-D85	506.29	3.24	3
B10-X00-M03(C01)-D93	559.34	3.81	1
B10-X00-M03(C01)-D94	493.28	3.58	1
B10-X00-M03(C01)-D80	567.31	3.92	1
B10-X00-M03(C01)-D117	533.33	3.77	1
B10-X00-M03(C01)-D34	567.31	3.99	1
B10-X00-M03(C01)-D87	567.31	4.21	1
B10-X00-M03(C01)-D108	634.35	4.07	1
B10-X00-M03(C01)-D91	533.29	4.01	1
B10-X00-M03(C01)-D114	602.35	4.1	1
B10-X00-M03(C01)-D14	515.32	4.64	1
B10-X00-M03(C01)-D141	552.31	4.34	1
B10-X00-M03(C01)-D109	580.34	4.89	1
B10-X00-M03(C01)-D107	531.26	3.56	1

Example 59

8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide tri-hydrochloride salt

[B10-X00-M03(C01)-D04]



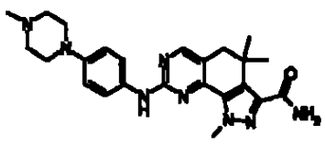


To 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (7.00 g, 15.192 mmol) dissolved into a 1:1 mixture of methanol/dichloromethane (149 mL) 4M hydrochloric

acid in dioxane (12.12 mL, 48.48 mL) was added and the solution stirred at room temperature for 2 hours. After removing the solvent under reduced pressure, the reddish solid was dried at 43°C under vacuum for 10 hours. There were obtained 8.11 g of the title compound as a red solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.69 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.85 (d, *J*=3.54 Hz, 3 H) 2.95 – 3.08 (m, 2 H) 3.10 – 3.26 (m, 2 H) 3.39 – 3.55 (m, 2 H) 3.74 (d, *J*=13.41 Hz, 2 H) 4.30 (s, 3 H) 7.00 (d, *J*=9.02 Hz, 2 H) 7.59 (d, *J*=8.90 Hz, 2 H) 8.16 (q, *J*=4.51 Hz, 1 H) 8.36 (s, 1 H) 9.44 (s, 1 H) 10.37 (s, 1 H)

Example 60



8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B10-X00-M03(C01)-D03]

To a suspension of 8-[4-(4-methyl-piperazin-1-yl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid potassium salt (185.5 mg, 0.382 mmol) in a 1:1 mixture of anhydrous tetrahydrofuranе and dimethylformamide (4.8 mL), N-ethyldiisopropylamine (0.13 mL, 0.760 mmol), 1-hydroxybenzotriazole ammonium salt (102 mg, 0.760 mmol) were added in that order. The reaction mixture was cooled to 0°C, treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (146 mg, 0.760 mmol) and then stirred at room temperature for 18 hours.

The reaction mixture was poured into water (10 mL) and the precipitate was filtered, washed with water, dried under vacuum at 40°C for 4 hours. There were obtained 130 mg (yield 76%) of pure title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.26 (s, 3 H) 2.46 – 2.56 (m, 4 H) 2.68 (s, 2 H) 3.04 – 3.14 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.29 (s, 1 H) 7.53 (d, *J*=9.15 Hz, 2 H) 7.55 (s, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)

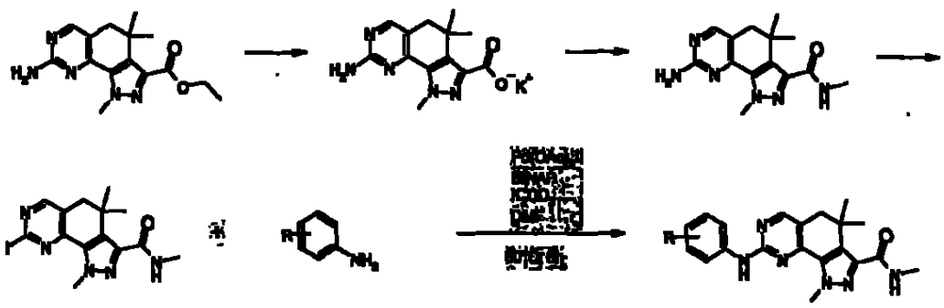
By working according to the above method the following compounds were prepared:

Table XIX

B04-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.71 (s, 2 H) 4.33 (s, 3 H) 6.97 (tt, *J* 7.38, 1.10 Hz, 1 H) 7.31 (m, 3 H) 7.56 (s, 1 H) 7.71 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.41 (s, 1 H) 9.52 (s, 1 H)

B12-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.72 (s, 2 H) 2.87 (d, *J* 4.63 Hz, 3 H) 3.35 (m, 8 H) 4.34 (s, 3 H) 7.21 (d, *J* 8.78 Hz, 1 H) 7.32 (s, 1 H) 7.56 (s, 1 H) 7.59 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.01 (d, *J* 2.44 Hz, 1 H) 8.43 (s, 1 H) 9.68 (s, 1 H) 10.39 (s, 1 H)
B13-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.73 (s, 2 H) 2.88 (d, *J* 4.63 Hz, 3 H) 3.32 (m, 8 H) 4.32 (s, 3 H) 7.33 (s, 1 H) 7.54 (d, *J* 8.90 Hz, 1 H) 7.56 (s, 1 H) 8.01 (dd, *J* 8.72, 2.38 Hz, 1 H) 8.12 (d, *J* 2.56 Hz, 1 H) 8.45 (s, 1 H) 9.86 (s, 1 H) 10.35 (s, 1 H)
B19-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.68 (s, 2 H) 3.00 – 3.13 (m, 4 H) 3.70 – 3.80 (m, 4 H) 4.31 (s, 3 H) 6.92 (d, *J*=9.02 Hz, 2 H) 7.29 (s, 1 H) 7.51 – 7.59 (m, 3 H) 8.34 (s, 1 H) 9.27 (s, 1 H)
B13-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 6 H) 2.86 (d, *J* 4.39 Hz, 3 H) 2.95 (s, 2 H) 3.34 (m, 8 H) 4.37 (s, 3 H) 7.21 (d, *J* 8.78 Hz, 1 H) 7.29 (s, 1 H) 7.45 (s, 1 H) 7.58 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.04 (d, *J* 2.44 Hz, 1 H) 8.53 (s, 1 H) 9.71 (s, 1 H) 10.49 (s, 1 H)
B12-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 6 H) 2.88 (d, *J* 4.39 Hz, 3 H) 2.96 (s, 2 H) 3.38 (m, 8 H) 4.35 (s, 3 H) 7.29 (s, 1 H) 7.46 (s, 1 H) 7.54 (d, *J* 8.90 Hz, 1 H) 8.00 (dd, *J* 8.66, 2.32 Hz, 1 H) 8.15 (d, *J* 2.44 Hz, 1 H) 8.55 (s, 1 H) 9.89 (s, 1 H) 10.32 (s, 1 H)
B04-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (s, 6 H) 2.95 (s, 2 H) 4.35 (s, 3 H) 6.98 (tt, *J* 7.35, 1.04, 0.98 Hz, 1 H) 7.27 (s, 1 H) 7.31 (dd, *J* 8.35, 7.50 Hz, 2 H) 7.47 (s, 1 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.51 (s, 1 H) 9.55 (s, 1 H)
B10-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.26 (s, 3 H) 2.47 (m, 4 H) 2.93 (s, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.32 Hz, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.53 (d, *J*=9.32 Hz, 2 H) 8.44 (s, 1 H) 9.28 (s, 1 H)

Example 61



Step 1. 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid potassium salt [B00-X00-M03(C01)-D02]

A suspension of ethyl 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (20.00 g, 66.368 mmol) in anhydrous ethanol (250 mL), 1.5M potassium hydroxide in ethanol (150 mL) was added under good stirring and the mixture was heated to reflux for 1.5 hours. After cooling in an ice bath, a solid was formed; that was filtered washing with ethanol, dried at 40°C under vacuum to yield 17.34 g (yield 84%) of white solid compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.51 (s, 2 H) 4.16 (s, 3 H) 6.37 (s, 2 H) 8.07 (s, 1 H)

Step 2. 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B00-X00-M03(C01)-D04]

To a suspension of 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid potassium salt (17.00 g, 54.594 mmol) in a 1:1 mixture of anhydrous tetrahydrofurane and dimethylformamide (340 mL), 2 M methylamine in tetrahydrofurane (40.80 mL, 81.60 mmol), 1-hydroxybenzotriazole (8.840 g, 65.418 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (12.540 g, 65.418 mmol) were added in that order, and the thick slurry was stirred at room temperature for 20 hours.

The reaction mixture was poured into water (2.5 L) and extracted with dichloromethane (4 x 250 mL). The combined organic extracts were washed with water (50 mL), dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure. There were obtained 17.0 g of yellowish solid that were triturated with diethylether to yield 13.05 g (yield 87%) of the desired compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.60 (s, 2 H) 2.75 (d, J=4.76 Hz, 3 H) 4.30 (s, 3 H) 6.55 (s, 2 H) 8.12 (q, J=4.39 Hz, 1 H) 8.17 (s, 1 H).

By working in an analogous way the following compounds were prepared:

8-amino-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide [B00-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.69 - 2.74 (m, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 2.94 (t, *J*=7.56 Hz, 2 H) 4.31 (s, 3 H) 6.54 (s, 2 H) 7.99 - 8.08 (m, 1 H) 8.18 (s, 1 H);

8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide [B00-X00-M03(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 2.61 (s, 2 H) 4.30 (s, 3 H) 6.57 (s, 2 H) 7.27 (s, 1 H) 7.51 (s, 1 H) 8.17 (s, 1 H)

Step 3, **8-Iodo-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide**

In a round bottom flask maintained under argon atmosphere, ethyl 8-amino-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (13.00 g, 45.400 mmol) was dissolved into anhydrous dimethoxyethane (800 mL); cesium iodide (11.795 g, 45.400 mmol), bisublimated iodine (5.761 g, 22.698 mmol), copper(I) iodide (2.594 g, 13.621 mmol), and *iso*-amyl nitrite (9.107 mL, 68.100 mmol) were added in that order and the mixture was heated to 70°C for 22 hours.

After cooling to room temperature, the solids materials were removed by suction filtration, washing with dichloromethane. The filtrate was concentrated to 400 mL, diluted with dichloromethane (1000 mL), washed with 30% ammonium hydroxide (100 mL), 5% sodium thiosulphate (50 mL), water (4 x 100 mL), and dried over anhydrous sodium sulphate. The solvent was removed under vacuum to afford 11.00 g of dark oil that was triturated with diethylether to yield 4.300 g of the title compound as a yellow solid. Purification of the mother liquors by flash chromatography on silica gel (eluant dichloromethane/methanol 97:3) afforded further 2.04 g of yellowish solid compound (overall yield 35%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.80 (s, 2 H) 4.24 (s, 3 H) 8.16 - 8.25 (m, 1 H) 8.48 (s, 1 H)

Step 4, **8-[3-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide** [B104-X00-M03(C01)-D04]

$Pd(OAc)_2$ (16.34 mg, 0.0728 mmol), (±)-BINAP (45.33 mg, 0.0728 mmol) and dimethylformamide (12 mL) were charged in a round-bottom flask flushed with argon. The mixture was stirred under argon for 30 minutes. Then 3-(4-methyl-piperazin-1-ylmethyl)-phenylamine (448.4 mg, 2.184 mmol), ethyl 8-iodo-1,4,4-trimethyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (300 mg, 0.728 mmol), K_2CO_3 (1.508 g, 10.910 mmol) and dimethylformamide (10 mL) were added. The resulting mixture was heated to 80°C in an oil bath under argon with good stirring for 3 hours.

After cooling to room temperature, the reaction mixture was filtered by suction filtration washing with dichloromethane and the filtrate was evaporated to dryness. The crude was purified by flash chromatography on silica gel (eluant: dichloromethane/methanol 95:5) to afford 215 mg (yield 62%) of pure title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.25 (s, 3 H) 2.42 (m, 4 H) 2.71 (s, 2 H) 2.77 (d, *J*=4.76 Hz, 3 H) 3.44 (m, 4 H) 3.48 (s, 2 H) 4.35 (s, 3 H) 6.91 (d, *J*=7.31 Hz, 1 H) 7.26 (t, *J*=7.68 Hz, 1 H) 7.56 (d, *J*=8.78 Hz, 1 H) 7.76 (s, 1 H) 8.15 (s, 1 H) 8.41 (s, 1 H) 9.5 (s, 1 H)

By working according to the above method the following compounds were prepared:

Table XX

B10-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.26 (s, 3 H) 2.44 - 2.54 (m, 4 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.04 - 3.13 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.84 Hz, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)
B09-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.13 (m, 4 H) 4.33 (s, 3 H) 6.59 (d, *J*=7.31 Hz, 1 H) 7.14 (t, *J*=7.68 Hz, 1 H) 7.23 (s, 1 H) 7.26 (d, *J*=8.78 Hz, 1 H) 8.15 (s, 1 H) 8.39 (s, 1 H) 9.33 (s, 1 H)
B101-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.55 - 3.62 (m, 13 H) 2.71 (s, 2 H) 2.75 - 2.79 (m, *J*=4.76 Hz, 3 H) 4.33 (s, 3 H) 7.25 (d, *J*=10.24 Hz, 2 H) 7.69 (d, *J*=7.80 Hz, 2 H) 8.10 - 8.18 (m, 1 H) 8.41 (s, 1 H) 9.55 (s, 1 H)
B19-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.02 - 3.09 (m, 4 H) 3.72 - 3.79 (m, 4 H) 4.31 (s, 3 H) 6.93 (d, *J*=9.02 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)

B107-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.06 - 3.13 (m, 4 H) 3.73 - 3.78 (m, 4 H) 4.33 (s, 3 H) 6.59 (dd, *J*=7.93, 2.07 Hz, 1 H) 7.16 (t, *J*=8.11 Hz, 1 H) 7.23 (t, *J*=2.01 Hz, 1 H) 7.30 (dd, *J*=7.74, 1.40 Hz, 1 H) 8.16 (q, *J*=4.59 Hz, 1 H) 8.39 (s, 1 H) 9.35 (s, 1 H)
B102-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.35 (s, 4 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.43 (s, 2 H) 3.58 (s, 4 H) 4.33 (s, 3 H) 7.25 (s, 2 H) 7.66 (s, 2 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B105-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 7 H) 2.38 (s, 4 H) 2.71 (s, 2 H) 2.77 (d, *J*=4.76 Hz, 3 H) 3.44 (s, 2 H) 3.58 (s, 5 H) 4.36 (s, 3 H) 6.87 - 6.99 (m, 1 H) 7.25 (t, *J*=7.56 Hz, 1 H) 7.58 (d, *J*=6.71 Hz, 1 H) 7.76 (s, 1 H) 8.41 (s, 1 H)
B103-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 1.64 - 2.07 (m, 4 H) 2.37 - 2.62 (m, 5 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.63 Hz, 3 H) 2.81 - 3.00 (m, 2 H) 4.30 (s, 3 H) 4.34 - 4.46 (m, 1 H) 6.94 (d, *J*=9.02 Hz, 2 H) 7.58 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.55 Hz, 1 H) 8.36 (s, 1 H) 9.34 (s, 1 H)
B106-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 1.70 - 2.18 (m, 4 H) 2.59 (s, 3 H) 2.71 (s, 2 H) 2.77 (d, *J*=4.76 Hz, 3 H) 2.93 - 3.50 (m, 4 H) 4.35 (s, 3 H) 4.40 - 4.57 (m, 1 H) 6.61 (dd, *J*=7.93, 2.07 Hz, 1 H) 7.21 (t, *J*=8.11 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.47 (s, 1 H) 8.12 - 8.19 (m, 1 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B120-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.24 (m, 6 H) 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.79 - 3.52 (m, 9 H) 4.31 (s, 3 H) 6.94 (d, *J*=8.78 Hz, 2 H) 7.55 (d, *J*=8.78 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)
B173-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.40 – 2.50 (m, 4 H) 2.68 (s, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 3.53 (s, 2 H) 3.60 (m, 4 H) 4.30 (s, 3 H) 6.98 (d, 1 H) 7.06 (dd, 1 H) 7.23 (d, 1 H) 8.14 (q, 1 H) 8.37 (s, 1 H) 9.39 (s, 1 H) 10 (bs, 1 H)

Reported below are the analytical HPLC/Mass data for some representative compounds of the invention

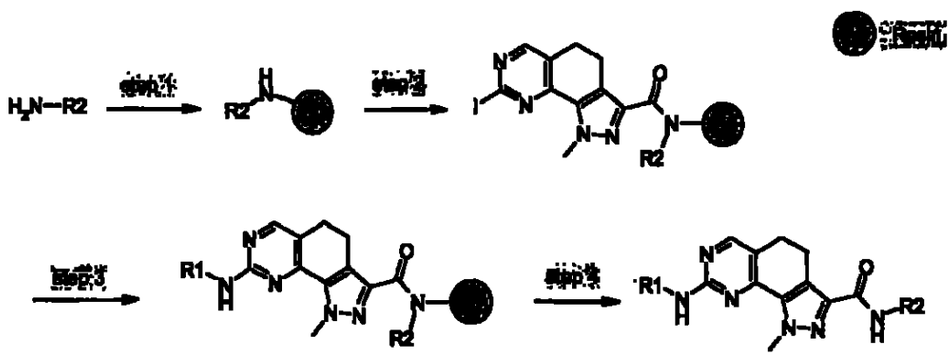
Table XXI

	M+H	RT	method
B121-X00-M03(C01)-D04	442.514	4.40	1
B122-X00-M03(C01)-D04	393.481	4.70	1
B123-X00-M03(C01)-D04	380.422	3.42	1

B124-X00-M03(C01)-D04	379.434	4.86	1
B125-X00-M03(C01)-D04	406.503	5.60	1
B126-X00-M03(C01)-D04	396.433	4.37	1
B127-X00-M03(C01)-D04	442.514	4.90	1
B128-X00-M03(C01)-D04	406.46	5.40	1
B114-X00-M03(C01)-D04	393.461	4.35	1
B129-X00-M03(C01)-D04	406.46	4.10	1
B11-X00-M03(C01)-D04	393.461	4.50	1
B130-X00-M03(C01)-D04	406.46	4.10	1
B131-X00-M03(C01)-D04	449.524	6.10	1
B168-X00-M03(C01)-D04	420.487	4.50	1
B132-X00-M03(C01)-D04	448.54	6.14	1
B133-X00-M03(C01)-D04	412.486	4.90	1
B134-X00-M03(C01)-D04	407.487	4.90	1
B135-X00-M03(C01)-D04	406.46	4.80	1
B21-X00-M03(C01)-D04	429.498	4.66	1
B136-X00-M03(C01)-D04	439.489	4.76	1
B137-X00-M03(C01)-D04	409.46	4.7	1
B138-X00-M03(C01)-D04	393.461	5.02	1
B139-X00-M03(C01)-D04	407.487	4.77	1
B140-X00-M03(C01)-D04	393.46	4.62	1
B141-X00-M03(C01)-D04	407.487	4.60	1
B142-X00-M03(C01)-D04	396.433	4.05	1
B143-X00-M03(C01)-D04	406.503	6.10	1
B144-X00-M03(C01)-D04	446.566	6.27	1
B145-X00-M03(C01)-D04	420.53	3.41	1
B17-X00-M03(C01)-D04	434.557	5.27	1
B146-X00-M03(C01)-D04	488.648	4.6	1
B147-X00-M03(C01)-D04	420.53	3.58	1
B148-X00-M03(C01)-D04	407.487	4.33	1
B149-X00-M03(C01)-D04	407.487	4.50	1
B150-X00-M03(C01)-D04	492.549	3.85	1
B151-X00-M03(C01)-D04	486.566	5.38	1
B152-X00-M03(C01)-D04	510.632	6.60	1
B153-X00-M03(C01)-D04	512.604	5.58	1
B154-X00-M03(C01)-D04	506.576	6.34	1
B155-X00-M03(C01)-D04	504.604	5.03	1
B156-X00-M03(C01)-D04	489.593	4.45	1
B13-X00-M03(C01)-D04	496.028	4.28	1
B117-X00-M03(C01)-D04	540.479	4.38	1
B157-X00-M03(C01)-D04	512.604	5.80	1
B158-X00-M03(C01)-D04	466.53	5.73	1
B159-X00-M03(C01)-D04	510.632	4.94	1
B160-X00-M03(C01)-D04	491.609	3.71	1
B161-X00-M03(C01)-D04	490.577	5.41	1
B162-X00-M03(C01)-D04	448.584	3.95	1
B163-X00-M03(C01)-D04	476.594	3.82	1
B164-X00-M03(C01)-D04	434.557	3.69	1
B165-X00-M03(C01)-D04	436.486	4.44	1
B109-X00-M03(C01)-D04	479.573	3.93	1

B166-X00-M03(C01)-D04	483.545	5.07	1
B12-X00-M03(C01)-D04	529.58	4.66	1
B167-X00-M03(C01)-D04	506.635	3.76	1

Example 62



Step 1 **Loading primary amines to a solid support (resin)**

A: Case where the "resin" is 4-(4-formyl-3-methoxyphenoxy)butyryl polyethylene glycol grafted aminomethylpolystyrene-1% DVB:

For each variant of R2 primary amine, 1 gram (0.39 mmol) of the aforementioned resin was charged to a 10 mL Argonaut Quest 210 reaction tube. Trimethyl orthoformate (7 mL) was added to the tube along with 5 equivalents (1.95 mmol) of each primary amine (indicated as R2 in the scheme). The reaction was mixed on the Quest at 25°C for 16 hours followed by a 2-hour period of heating at 70°C. After cooling and removal of the reaction solution, the resin was washed once with trimethyl orthoformate (7 mL each) and three times with anhydrous methanol (7 mL). Anhydrous methanol (5 mL) was then added to the resin, followed by the addition of 148 mg (3.9 mmol, 10 equiv) of sodium borohydride. After vigorous gas evolution had ceased, the tube was capped and mixed for 8 hours at room temperature. The resin was washed 3 times with methanol (5 mL), three times with methanol/water (1:1, 5 mL), and three times with DMF (5 mL). The resin was then treated with 20% piperidine in DMF for 1 hour at room temperature. Again, the resin was washed three times with DMF (5 mL), three times with methanol (5 mL), and three times with dichloromethane (5 mL). A sample of the resin was tested for quantitative amine loading by using the Fmoc UV-spectrometric method described below. Qualitatively, the resin was analyzed using the chloranil test method described below.

B: Case where the "resin" is Rink amide, 4-(2',4'-dimethoxyphenyl-fmoc-aminomethyl)phenoxy (copolystyrene-1% DVB):

1 g (0.39 mmol) of the aforementioned resin were charged into a 10 mL Argonaut Quest 210 reaction tube. The resin was treated with 20% piperidine in DMF for 5 minutes and a then a second treatment occurred for 30 minutes at room temperature. The resin was washed with DMF (3 x 5 mL), with methanol (3 x 5 mL) and with dichloromethane (3 x 5 mL).

Quantitative amine loading by using the Fmoc UV-spectrometric method:

A precisely tarred quantity (25 mg ± 5 mg) of dry, loaded resin was charged into a 3 mL polypropylene syringe, fitted with a filter disk. To the syringe, 3 equivalents of 9-fluorenylmethyl chloroformate dissolved in 1 mL of dichloromethane were charged and 1.5 equivalents of N,N-diisopropylethylamine were then added. The resin was shaken by means of orbital shaker, for 1 hour. The resin was washed with DMF (3 x 2 mL, 5 min.), with methanol (3 x 2 mL, 5 min.), and with DCM (3 x 2 mL, 5 min.).

1 mL of a 20% piperidine solution in DMF was drwan from the syringe and agitated for 5 minutes at room temperature. The solution was dispensed into a 10 mL volumetric flask. A second aliquot of the 20% piperidine solution in DMF was drawn and agitated for 30 minutes at room temperature. Again, the solution was dispensed into the same 10 mL volumetric flask (stock solution). DMF was added to the volumetric flask to achieve a 10 mL total volume. This volumetric flask containing the stock solution was agitated thoroughly and exactly 0.5 mL were transferred into a second 10 mL volumetric flask (test solution). Again, DMF was added to the volumetric flask up to a 10 mL total volume. The absorbance of this test solution was measured through an *Amersham Pharmacia Biotech Ultrospec 3000 Pro*, UV-Vis spectrometer at λ=302nm against DMF as the blank. The post reaction resin substitution was calculated using the following formula:

$$loading\ (mmol/g) = (A_{302} \times 20\ fold \times 10\ mL) / 8100 \times wt$$

where A_{302} is the UV absorbance at λ=302nm, ε=8100 is the extinction coefficient of the piperidine-fluorenone adduct and *wt* is the tare of the resin in milligrams.

Qualitative chloranil (3,4,5,6-tetrachloro-1,2-benzoquinone) test for resin bound secondary amines: A small aliquot of pre-washed resin containing the attached amine

was placed in a micro-test tube. The beads were washed once with acetone and the solvent was removed by decantation. One drop of the chloranil test solution was added to the test tube and allowed to stand at room temperature for 5 minutes. A dark green to brown color was a positive indication of a secondary amine. The intensity of the color was a non-quantitative indication of secondary amine concentration.

Test solution: a saturated solution of 3,4,5,6-tetrachloro-1,2-benzoquinone in toluene at room temperature.

Step 2 Acylation of the solid supported amine with 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carbonyl fluoride

For each variant of R2 primary amine loaded onto 1 g (0.39 mmol) of the resin in step 1 above, the following pre-activated carboxylic acid fluoride reagent was added. In 5 mL of dichloromethane, 166 mg (0.47 mmol, 1.2 equivalents) of 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate, 155 mg (0.585 mmol, 1.5 equivalents) of tetramethylfluoroformamidinium hexafluorophosphate and 0.102 mL (0.585 mmol, 1.5 equivalents) of N,N-diisopropylethylamine were dissolved. N,N-Dimethylacetamide was added dropwise to the solution until all reagents were in solution with sonication. The reaction system was stirred at room temperature for 30 minutes. Additional 0.102 mL (0.585 mmol, 1.5 equivalents) of N,N-diisopropylethylamine were added to the solution, in 30 minutes, and the entire content was charged to the resin on the Quest 210 synthesizer. The resin was mixed for 18 hours at room temperature. The resin was drained of the acylation cocktail and washed with DMF (3 x 5 mL, 5 min.), with methanol (3 x 5 mL, 5 min.) and with DCM (3 x 5 mL, 5 min.). The resin was dried from DCM under vacuum. The resin was qualitatively tested for the acylation reaction completion using the chloranil test method. A sample of each dried resin was subjected to the quantitative Fmoc UV-spectrometric analysis to determine the extent of resin bound acylation.

Step 3 Catalytic amination of the solid supported 8-iodo-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide

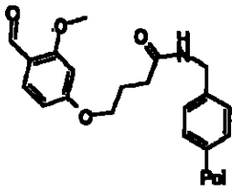
Using a 4 mL Argonaut Trident synthesizer cassette, 200 mg (0.078 mmol) of each resin type from step 2 above, were charged into separate vials. To each of the reactor vials flushed with argon, potassium carbonate (0.158 g, 1.56 mmol), palladium acetate [$Pd(OAc)_2$] (1.8 mg, 0.008 mmol, 10%), (±)-BINAP (5.0 mg, 0.008 mmol, 10%) and

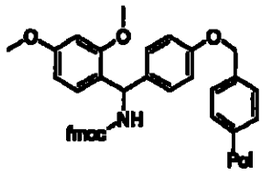
the corresponding R1 amine (0.156 mmol, 2 equivalents) in dimethyacetamide (2 mL) were added. The resulting mixture was agitated at room temperature for 1 hour and then heated to 60°C for 16 hours on the Argonaut Trident External Agitation Thermal Unit (EATU) synthesis station.

The resin was drained from the synthesis cocktail and washed using the Argonaut Trident EATU synthesis station with DMF (1 x 2 mL, 5 min.), with water (1 x 2 mL, 5 min.), with DMF/water (1:1) (3 x 2 mL, 5 min.), with DMF (3 x 2 mL, 5 min.), with methanol (3 x 2 mL, 5 min.) and with DCM (3 x 2 mL, 5 min.).

Step 4 Cleavage of the differentially substituted 8-amino-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide from the solid support

To each Argonaut Trident reactor vial, 2 mL of the following resin cleavage cocktail were added: dichloromethane (50 mL), trifluoroacetic acid (49 mL) and water (1 mL). The resin suspended in the cleavage cocktail was shaken for 1 hour at room temperature on the Argonaut Trident EATU synthesis station. The solution containing the crude products was captured into separate vials where three additional resin washing with dichloromethane (2 mL each) were also captured to the same corresponding vials.





4-(1-formyl-3-methoxyphenoxy)butyryl polyethylene glycol grafted aminomethylpolystyrene (4-FPB-PEG-PS)

(2,4-dimethoxyphenyl)-fmoc-aminomethylpolystyrene (carboxylated 4-SAL-PS)

Example 63

N-[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]guanidine

Step 1. 1,3-bis(tert-butoxycarbonyl)guanidine



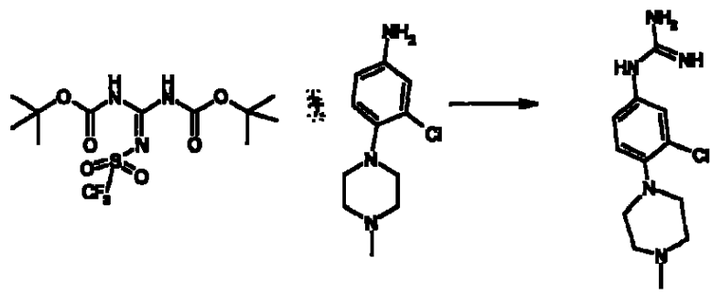
15 g of 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (0.052 mol) were suspended in 150 mL of gaseous ammonia in methanol and the mixture was stirred at room temperature in a close bottle at room temperature. The resulting solution was concentrated in vacuo until 10 g (74% yield) of the title compound precipitated which were collected by filtration.

Step 2. 1,3-bis(tert-butoxycarbonyl)-2-trifluoromethanesulfonylguanidine



A solution of 5.2 g (20 mmol) of 1,3-bis(tert-butoxycarbonyl)guanidine in 100 mL of dry dichloromethane was cooled to –78°C under stirring and 5.6 g (20 mmol) of trifluoromethanesulfonic anhydride were added dropwise. The reaction mixture was allowed to come to room temperature and stirred for 5 hours. An aqueous solution of $NaHSO_4$ was added and the organic layer dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography on a silica gel column (eluant petroleum ether/ethyl acetate 7/3) to give 4.0 g (51% yield) of the title compound.

Step 3. N-[3-chloro-4-(4-methylpiperazin-1-yl)phenyl]guanidine



To a solution of 3.0 g (13.3 mmol) of 4-(3-chloro-4-methylpiperazin-1-yl)aniline and 2.22 mL (16.0 mmol) of triethylamine in 36 mL of dichloromethane, 6.0 g (15.3 mmol) of 1,3-bis(tert-butoxycarbonyl)-2-trifluoromethanesulfonylguanidine were added. The reaction mixture was stirred at room temperature for 72 hours. The solution was diluted with further dichloromethane, washed with water and the solvent dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography on a silica gel column (eluant dichloromethane/methanol 92/8) giving 5.4 g (86.2% yield) of a protected intermediate, that was treated with 60 mL of 4 N HCl in dioxane. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue redissolved in water, the resulting solution neutralized and the product extracted with ethyl acetate. The solvent was removed under reduced pressure to give 2.4 g (78.7% yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 2.48 (m, 4 H) 2.90 (m, 4 H) 5.38 (bs, 4 H) 6.72 (dd, *J* 2.44, 8.42 Hz, 1 H) 6.82 (d, *J* 2.44, 1 H) 7.01 (d, *J* 8.42 Hz, 1 H).

By working analogously, but employing the suitable substituted aniline derivative, the following compounds were prepared:

N-[3-(4-methylpiperazin-1-yl)phenyl]guanidine;

N-[4-(4-methylpiperazin-1-yl)phenyl]guanidine;

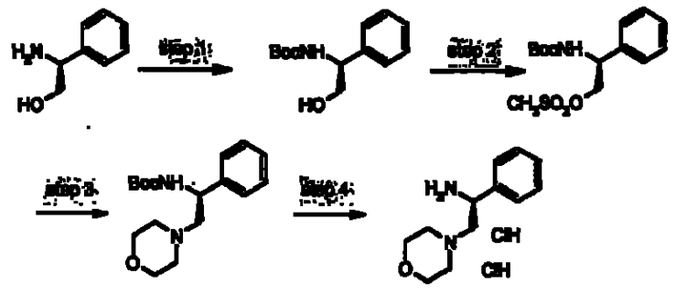
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (s, 3 H) 7.09 (m. 4 H) 7.41 (s, 2 H) 9.85 (s, 1 H) 11.39 (s, 1 H) (as dihydrochloride);

N-[4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)phenyl]guanidine;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.43 (m, 4 H) 2.80 (m, 4 H) 5.46 (bs, 4 H) 7.02 (m, 2 H) 7.37 (d, 1 H, J 8.42 Hz);

N-(3-chlorophenyl)guanidine.

Example 64



Step 1. Tert-butyl (1S)-2-hydroxy-1-phenylethylcarbamate

A solution of 40 g (0.291 mol) of (2S)-2-amino-2-phenylethanol in 1250 mL of ethylacetate and 99.83 mL (0.583 mol) of N-ethyl-N,N-diisopropylamine was cooled to 0°C and 76.21 g (0.349 mol) of di-tert-butyl dicarbonate were added portionwise. The mixture was stirred at room temperature for 3 hours then it was washed with 400 mL of 1M $KHSO_4$. The organic layer was dried over Na_2SO_4 thus affording 69.88 g of the title compound.

Step 2. (2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylethyl methanesulfonate

The solution of 68.9 g (0.29 mol) of tert-butyl (1S)-2-hydroxy-1-phenylethylcarbamate and triethylamine (40.36 mL, 0.29 mol) in 700 mL of dry dichloromethane under inert atmosphere was cooled to −10°C and 24.79 mL (0.319 mol) of mesylchloride were added dropwise. After 2 hours at 0°C the mixture was poured into ice and water and

extracted with dichloromethane. The organic phase was washed with diluted HCl, aqueous $NaHCO_3$, brine and dried over Na_2SO_4 yielding 89.8 g of the product (98 % yield).

Step 3. Tert-butyl (1S)-2-morpholin-4-yl-1-phenylethylcarbamate

The mixture of 25 g (0.0792 mol) of (2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylethyl methanesulfonate and morpholine (69.37 mL, 0.792 mol) in 250 mL of dry THF under inert atmosphere was refluxed for 8 hours. The reaction was then cooled to room temperature, treated with diethylether and the solid filtered. The solution was evaporated affording the crude as a yellow oil that was purified through silica gel chromatography (eluant hexane/ethylacetate 6/4). 11.59 g of the title product were isolated (48 % yield).

Step 4. (1S)-2-morpholin-4-yl-1-phenylethanamine dihydrochloride

A solution of 11.58 g (0.0378 mol) of tert-butyl (1S)-2-morpholin-4-yl-1-phenylethylcarbamate in 100 mL of dichloromethane was treated with 120 mL of HCl 4M in dioxane and stirred for 18 hours. The mixture was diluted with diethylether and the product filtered (9.48 g, 90 % yield).

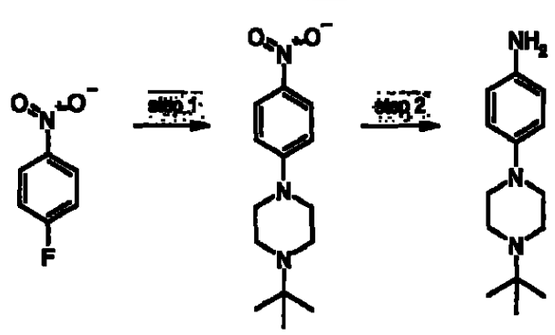
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.37 (m, 6 H) 3.83 (m, 4 H) 4.90 (m, 1 H) 7.51 (m, 5 H) 8.84 (bs, 3 H).

By working analogously the following compounds was prepared:

(1S)-2-(4-methylpiperazin-1-yl)-1-phenylethanamine trihydrochloride

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (m, 13 H) 4.47 (m, 1 H) 7.46 (m, 5 H) 8.45 (bs, 3 H) 10.40 (bs, 1 H).

Example 65



Step 1 1-tert-butyl-4-(4-nitrophenyl)piperazine

A solution of 800 mg (5.67 mmol) of 1-fluoro-4-nitrobenzene, 2.07 g (1.2 mmol) of 1-tert-butylpiperazine dihydrobromide and 3.2 mL (20.41 mmol) of triethylamine, in 22 mL of acetonitrile, was refluxed for 10 hours. The mixture was cooled to room temperature, diluted with water and extracted with dichloromethane. The organic layer was washed with water and brine, dried over Na_2SO_4 and evaporated. Purification by flash chromatography (eluant dichloromethane/methanol 7/3) yielded 860 mg of the title compound as yellow solid.

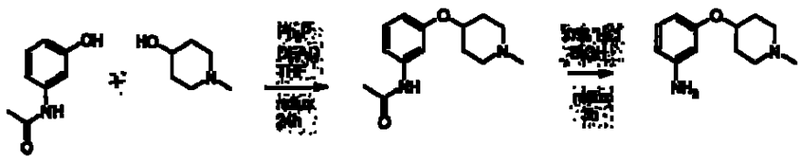
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 9 H) 2.63 (m, 4 H) 3.43 (m, 4 H) 7.03 (d, 2 H) 8.05 (d, 2 H).

Step 2. 4-(4-tert-butylpiperazin-1-yl)phenylamine

To a solution of 840 mg (3.189 mmol) of 1-tert-butyl-4-(4-nitrophenyl)piperazine in 24 mL of methanol, 904 mg (16.9 mmol) of ammonium chloride dissolved in 6 mL of water and 552 mg (9.886 mmol) of iron were added. After 7 hours, the suspension was cooled and filtered. pH was adjusted to 10 through portionwise addition of Na_2CO_3 to the aqueous phase. Extraction with dichloromethane yielded 667 mg of the title amine.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 9 H) 2.62 (m, 4 H) 2.89 (m, 4 H) 4.52 (s, 2 H) 6.50 (d, *J*=8.78 Hz, 2 H) 6.67 (d, *J*=8.78 Hz, 2 H).

Example 66



N-[3-(1-Methyl-piperidin-4-yloxy)-phenyl]-acetamide

A suspension of N-(3-Hydroxy-phenyl)-acetamide (30.2 g) in anhydrous tetrahydrofuran (600 mL) was treated with 4-hydroxy-N-methylpiperidine (30.54 mL) and triphenylphosphine (68.18 g); a solution of diethylazadicarboxylate in anhydrous tetrahydrofuran (THF) (40.94 mL in 60 mL of THF) was added dropwise and the mixture was stirred at room temperature for 2 hours and then heated to 50°C overnight. Further amounts of triphenylphosphine (28.00 g) and diethylazadicarboxylate (14 mL) were added and the heating was continued for additional 24 hours.

The solvent was removed under vacuum and the residue was taken up with ethyl acetate (600 mL), and extracted with 2N hydrochloric acid (3 x 200 mL). The aqueous layer was washed with ethyl acetate and pH was brought to 10 by addition of 20% sodium

hydroxide. Extraction with ethyl acetate (4 x 100 mL) was carried out and the combined organic extracts were washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude was purified by flash chromatography on silica gel (eluant dichloromethane/methanol 85:15 then + 0.1% triethylamine) to yield 21 g of the desired compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 - 1.68 (m, 2 H) 1.83 - 1.96 (m, 2 H) 2.01 (s, 3 H) 2.14 (s, 3 H) 2.46 - 2.52 (m, 2 H) 2.52 - 2.63 (m, 2 H) 4.18 - 4.20 (m, 1 H) 6.59 (d, 1 H) 7.05 (d, 1 H) 7.14 (t, 1 H) 7.26 (s, 1 H) 9.83 (s, 1 H).

3-(1-Methyl-piperidin-4-yloxy)-phenylamine

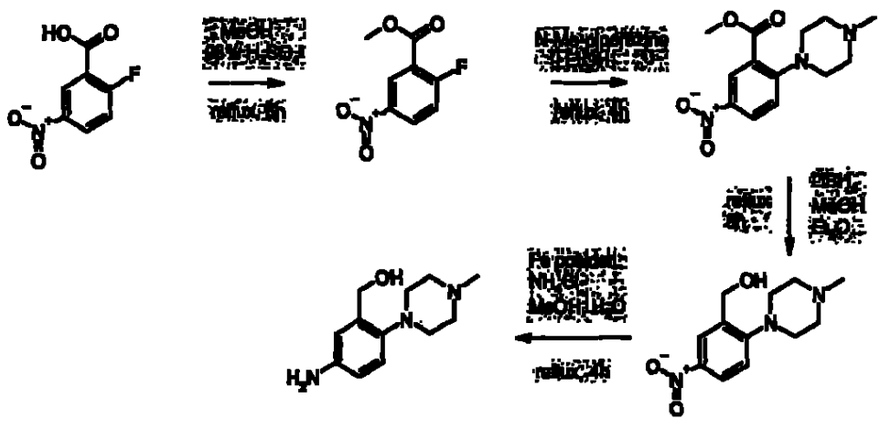
A solution of N-[3-(1-Methyl-piperidin-4-yloxy)-phenyl]-acetamide (2.604 g) in absolute ethanol (40 mL) was treated with 37% hydrochloric acid and the solution was heated to reflux for 3 hours.

After removing the solvent under vacuum, the residue was dissolved in water and washed with ethyl acetate (30 mL). The aqueous solution was basified by 20% sodium hydroxide and extracted with ethyl acetate (4 x 50 mL); the combined organic layers were washed with brine (4 x 20 mL), with water (2 x 10 mL) and dried over anhydrous sodium sulphate. After removing the solvent, the crude (2.00 g) was crystallized from n-hexane and ethyl acetate to yield 1.00 g of pure compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 - 1.68 (m, 2 H) 1.82 - 1.94 (m, 2 H) 2.12 - 2.27 (m, 2 H) 2.21 (s, 3 H) 2.58 - 2.71 (m, 2 H) 4.14 - 4.29 (m, 1 H) 4.98 (s, 2 H) 6.09 (ddd, *J*=8.11, 2.32, 0.79 Hz, 1 H) 6.14 (ddd, *J*=7.83, 2.04, 0.98 Hz, 1 H) 6.16 (t, *J*=2.19 Hz, 1 H) 6.88 (t, *J*=7.99 Hz, 1 H)

Example 67

5-Amino-2-(4-methyl-piperazin-1-yl)-phenyl]-methanol



Methyl 2-fluoro-5-nitro-benzoate

A solution of 2-fluoro-5-nitro-benzoic acid (3.702 g, 20 mmol) in anhydrous methanol (10.00 mL) was treated with 98% sulphuric acid and the solution was heated to reflux for 4 hours. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (50 mL). The solution was washed with saturated aqueous sodium bicarbonate (3 x 10 mL), brine until neutrality ant then water, and dried over anhydrous sodium sulphate. The solvent was removed under vacuum to afford a thick oil that started to crystallize. After adding n-hexane (3 mL) the crude was stored for 2 days in the fridge. The crystalline compound was filtered and washed with n-hexane to yield 3.147 g of the pure compound.

By concentrating the mother liquors a second crop was obtained (390 mg) (y = 89%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 7.69 (m, 1 H) 8.55 (m, 1 H) 8.65 (m, 1 H).

Methyl 2-(4-methyl-piperazin-1-yl)-5-nitro-benzoate

A solution of methyl 2-fluoro-5-nitro-benzoate (3.487 g, 17.511 mmol) and N-methylpiperazine (3.855 mL, 3.508 g, 35.022 mmol) in 30 mL of anhydrous methanol was heated to reflux for 5 hours.

After removing the volatiles at reduced pressure, the crude orange oil was treated slowly with water (about 20 mL) and stirred in an ice bath for 1 hour. The crystalline compound formed was filtered by suction filtration, washed with water and dried at 40°C under vacuum for 24 hours. There were obtained 4.627 g of yellow compound (y = 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.46 (m, 4 H) 3.27 (m, 4 H) 3.87 (s, 3 H) 7.22 (d J=9.27 Hz, 1 H) 8.08 (dd J=9.27 Hz J=2.80 Hz, 1 H) 8.33 (d J=2.80 Hz, 1 H).

2-(4-Methyl-piperazin-1-yl)-5-nitro-phenyl]-methanol

A suspension of methyl 2-(4-methyl-piperazin-1-yl)-5-nitro-benzoate (1.40 g, 5.00 mmol) in anhydrous diethyl ether (60 mL) was treated with litium borum hydride (190.5 mg, 8.75 mmol) and the formation of a precipitate was observed. Anhydrous methanol (0.350 mL, 280.3 mg, 8.75 mmol) was then added and the solution heated to reflux for 2 hours. As the reaction was not complete, further litium borum hydride (190.5 mg) and methanol (0.350 mL) were added twice every 4 hours.

After cooling in ice bath, the reaction mixture was treated with water, with 1N HCl (6 mL) and stirred at room temperature for 15 minutes. The solution was then basified to pH 11 by 1N sodium hydroxide and extracted with dichloromethane; the organic extracts were washed with brine and with water and dried over anhydrous sodium sulphate. The solvent was evaporated to dryness to afford 1,35 g of a brownish solid that was purified by flash chromatography on silica gel (eluant dichloromethane/methanol 95:5) to yield 1,10 g of desired compound (y = 87%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.52 (m, 4 H) 3.03 (m, 4 H) 4.54 (m, 2 H) 5.53 (t, 1 H) 7.17 (d J=8.90 Hz, 1 H) 8.08 (dd J=8.90 Hz J=2.92 Hz, 1 H) 8.33 (d J=2.92 Hz, 1 H).

5-Amino-2-(4-methyl-piperazin-1-yl)-phenyl]-methanol

To a solution of crude [2-(4-Methyl-piperazin-1-yl)-5-nitro-phenyl]-methanol (437 mg, 1.74 mmol) in methanol (1.5 mL), ammonium chloride (NH_4Cl) (465 mg), water (4.9 mL) and Fe powder (290 mg) were added and the mixture was heated at 100°C for 3 hours.

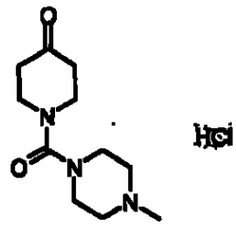
The reaction mixture was filtered and the black precipitate washed with MeOH/water 1:1 (10 mL). Methanol was removed under vacuum and the remaining water was basified with sodium carbonate (Na_2CO_3) and extracted with ethyl acetate (5 x 20 mL). The organic extracts were washed with brine (2 x 10 mL) and with water (2 x 5 mL) and dried over anhydrous sodium sulphate. After evaporation, the resultant crude orange solid was purified by flash chromatography on silica gel (eluant

dichloromethane/methanol/triethylamine 90:10:0.1) to yield 357 mg of pure title compound (y = 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.73 (m, 4 H) 4.48 (m, 2 H) 4.75 (bs, 2 H) 4.95 (t, 1 H) 6.43 (dd J=8.42 Hz J=2.68 Hz, 1 H) 6.67 (d J=2.68 Hz, 1 H) 6.80 (d J=8.42 Hz, 1 H).

Example 68

1-(4-Methyl-piperazine-1-carbonyl)-piperidin-4-one hydrochloride

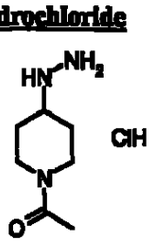


To a suspension of 4-methylpiperazine-1-carbonyl chloride hydrochloride (19.9 g 0.1 mol) and piperidone monohydrate hydrochloride (15.3 g 0.1 mol), in 200 mL of dichloromethane, dry triethylamine (45 mL, 0.33 mol) was added dropwise. The mixture was stirred for 2 hours. The organic phase was washed with brine (2 x 20 mL) and dried over sodium sulfate. After filtration, the solvent was evaporated in vacuo and the crude product was dissolved in EtOH (50 mL) and diethylether (100 mL) and treated with HCl 4N in dioxane (25 mL). After 1 hour, the precipitate was filtered and dried in oven to give 13 g (yield 50%) of the title compound.

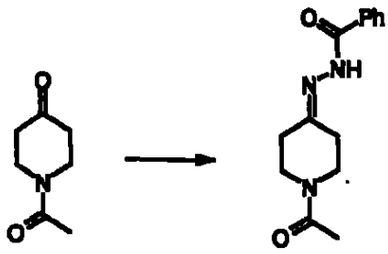
1 H NMR (400 MHz, DMSO-D6) δ ppm 2.40 (t, *J*=6.16 Hz, 4 H) 2.81 (s, 3 H) 3.00 - 3.11 (m, 2 H) 3.12 - 3.23 (m, 2 H) 3.28 - 3.42 (m, 2 H) 3.51 (t, *J*=6.16 Hz, 4 H) 3.73 (d, *J*=14.27 Hz, 2 H) 10.12 (s, 1 H)

Example 69

1-acetyl-4-hydrazinopiperidine hydrochloride



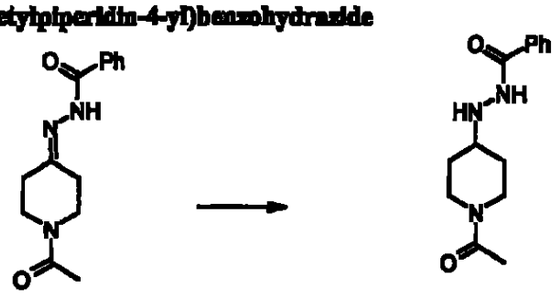
Step 1: N'-(1-acetylpiperidin-4-ylidene)benzohydrazide



20 g (0.142 mol) of 1-acetyl-4-piperidone were dissolved in 400 mL of absolute ethanol and 21.2 g (0.156 mol) of benzoylhydrazine were added. The resulting solution was refluxed for 6 hours under stirring. The solvent was then removed in vacuo and the residue partitioned between dichloromethane and water. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was triturated with diethylether and 30 g (83 % yield) of the title compound were collected by filtration.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.07 (s, 3 H) 2.43-2.62 (m, 4 H) 3.45-3.74 (m, 4 H) 7.51 (m, 3 H) 7.84 (m, 2 H) 10.7 (bs, 1 H).

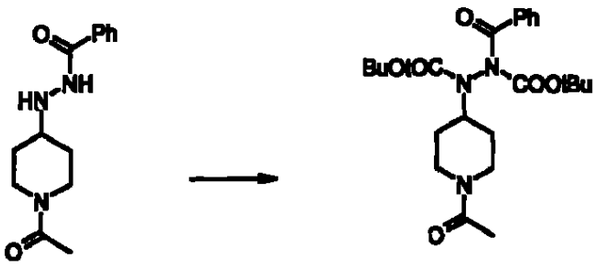
Step 2: N'-(1-acetylpiperidin-4-yl)benzohydrazide



30 g (0.12 mol) of N'-(1-acetylpiperidin-4-ylidene)benzohydrazide were dissolved in 500 mL of glacial acetic acid and 1 g of PtO_2 were added. The mixture was hydrogenated at 40 psi for 12 hours at room temperature. The catalyst was then filtered on celite and the filtrate evaporated in vacuo. The residue was redissolved with dichloromethane and washed with aqueous $NaHCO_3$. The solvent was dried over sodium sulfate and removed under reduced pressure to give, after trituration with diethylether, 28.6 g (92 % yield) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (m, 2 H) 1.81 (m, 2 H) 2.00 (s, 3 H) 3.75 (m, 2 H) 4.10 (m, 2 H) 4.19 (s, 1 H) 7.49-7.51 (m, 3 H) 7.84 (m, 2 H) 10.01 (s, 1 H).

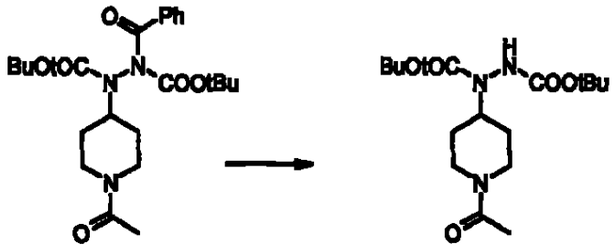
Step 3: di-tert-butyl 1-(1-acetylpiperidin-4-yl)-2-benzoylhydrazine-1,2-dicarboxylate



To a solution of 28.6 g (0.11 mol) of N'-(1-acetylpiperidin-4-yl)benzohydrazide in 700 mL of acetonitrile, 53.19 g (0.44 mol) of 4-dimethylaminopyridine (DMAP) and 77.2 g (0.35 mol) of di-tert-butyldicarbonate were added. The mixture was stirred overnight, the solvent removed and the residue taken up with dichoromethane and washed with aqueous $KHSO_4$ to remove DMAP. The organic layer was dried over sodium sulfate and evaporated to give 45 g of the title compound as an oil.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 and 1.40 (2s, 18H) 1.97 (s, 3 H) 4.28 (m, 1 H) 7.51-7.53 (m, 4 H).

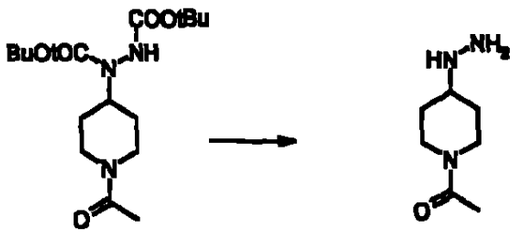
<u>Step 4:</u> di-tert-butyl 1-(1-acetylpiperidin-4-yl)hydrazine-1,2-dicarboxylate



45 g (0.1 mol) of di-tert-butyl 1-(1-acetylpiperidin-4-yl)-2-benzoylhydrazine-1,2-dicarboxylate were dissolved in 1 L of tetrahydrofuran and a solution of 5.8 g (0.14 mol) of lithium hydroxide monohydrate in 1 L of water were added. The mixture was stirred at room temperature for 16 hours, the tetrahydrofuran removed in vacuo and the aqueous layer extracted several times with dichloromethane. The organic phase was dried over sodium sulfate and evaporated to dryness, giving 32 g (84 % yield) of the title compound.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 and 1.42 (2s, 18H) 1.99 (s, 3 H) 4.09 (m, 1 H) 2.52 and 3.05 /2m, 4 H) 3.95 and 4.41 (2m, 4 H) 8.81 (bs, 1 H).

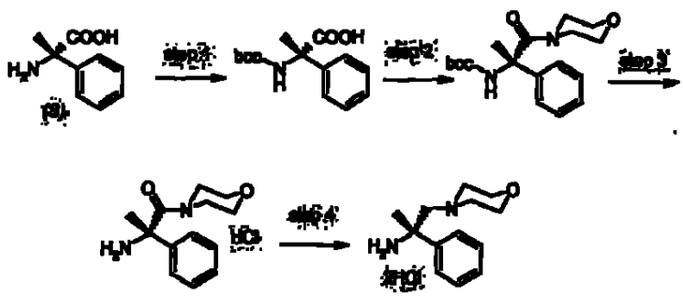
<u>Step 5:</u> 1-acetyl-4-hydrazinopiperidine hydrochloride



32 g (0.09 mol) of di-tert-butyl 1-(1-acetylpiperidin-4-yl)hydrazine-1,2-dicarboxylate were dissolved in 300 mL of methanol and 30 mL of HCl 4 M in dioxane were added. The mixture was stirred at room temperature overnight. The solvent was then evaporated and the residue crystallized from ethanol, giving 14 g (77 % yield) of the title compound.

Example 70

(1S)-1-methyl-2-morpholin-4-yl-1-phenylethylamine dihydrochloride



Step 1. N-(tert-butoxycarbonyl)-2-phenyl-D-alanine

To a suspension of 500 mg of 2-phenyl-D-alanine (3.02 mmol) and trimethylammonium hydroxide (aqueous solution 10%, 2.8 mL, 3.02 mmol) in 15 mL of acetonitrile, diterbutylcarbonate (1.047 g, 4.8 mmol) was added and the mixture was stirred at room temperature for 2 days. The solvent was then removed under vacuo, the residue was dissolved in water and washed with diethylether. The aqueous layer was acidified to pH = 3-4 with citric acid and the product was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with water, dried over Na_2SO_4 and evaporated. The title product was recovered as white solid (630 mg, yield 78 %).

Step 2. N-(tert-butoxycarbonyl)-(1S)-1-methyl-2-morpholin-4-yl-2-oxo-1-phenylethylamine

630 mg (2.374 mmol) of N-(tert-butoxycarbonyl)-2-phenyl-D-alanine were dissolved in 20 mL of dry DMF and O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium

tetrafluoborate (TBTU, 1.37 g, 4.27 mmol), morpholine (0.412 mL, 4.73 mmol) and diisopropylethylamine (1.63 mL, 9.5 mol) were added. The mixture was stirred at room temperature for 1 hour, then the solvent was removed and the residue dissolved with dichloromethane. The solution was washed with saturated $NaHCO_3$, brine, water and dried over Na_2SO_4. 700 mg of the title compound were recovered (88% yield).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (s, 9 H) 1.65 (s, 3 H) 3.33 (m, 8 H) 7.35 (m, 6 H).

Step 3. (1S)-1-methyl-2-morpholin-4-yl-2-oxo-1-phenylethylamine hydrochloride.

A solution of 630 mg (1.884 mmol) of N-(tert-butoxycarbonyl)-(1S)-1-methyl-2-morpholin-4-yl-2-oxo-1-phenylethylamine in 20 mL of dioxane was treated with 2.5 mL of HCl 4N in dioxane overnight. The solvent was removed under vacuo and the solid was triturated with diethylether yielding 560 mg of the title compound.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (s, 3 H) 3.35 (m, 8 H) 7.51 (m, 5 H) 8.52 (bs, 3 H).

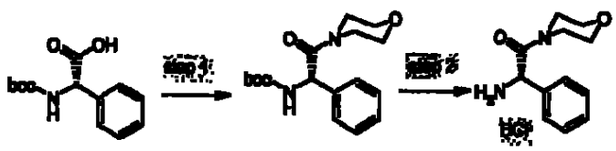
Step 4. (1S)-1-methyl-2-morpholin-4-yl-1-phenylethylamine dihydrochloride.

Under an argon atmosphere 412 mg of (1S)-1-methyl-2-morpholin-4-yl-2-oxo-1-phenylethylamine hydrochloride (1.522 mol) were dissolved in 30 mL of dry THF. A 2 M solution of borane dimethylsulfide (4.4 mL, 5.78 mmol) was added dropwise at 0°C and the mixture stirred for 10 minutes at 0°C and then allowed to reach room temperature (gas evolution). After 4 hours the reaction was quenched with methanol (added very carefully) and diluted with methanol when effervescence ceased. THF was removed under vacuo and the methanolic solution was heated at 60°C for 30 minutes. The solvent was at last completely removed recovering 330 mg of the amine that was subsequently dissolved in 15 mL of dioxane and treated with 1.35 mL of HCl 4 N in dioxane. After 1 hour the solvent was evaporated and the product was triturated with diethylether to yield 350 mg of the expected salt.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 (s, 3 H) 2.52 (m, 6 H) 3.57 (m, 4 H) 7.51 (m, 5 H) 8.53 (s, 3 H).

Example 71

(1S)-2-morpholin-4-yl-2-oxo-1-phenylethylamine hydrochloride



Step 1. N-(tert-butoxycarbonyl)-(1S)-2-morpholin-4-yl-2-oxo-1-phenylethylamine

1 g (3.98 mmol) of Boc-L-phenylglicine was dissolved in 18 mL of dry DMF and O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoborate (TBTU, 1.92 g, 5.97 mmol), morpholine (0.555 mL, 6.37 mmol) and diisopropylethylamine (2.72 mL, 15.92 mol) were added. The mixture was stirred at room temperature for 1 hour, then the solvent was removed and the residue dissolved with dichloromethane. The solution was washed with saturated $NaHCO_3$, brine, water and dried over Na_2SO_4. 1.327 g of the title compound were recovered.

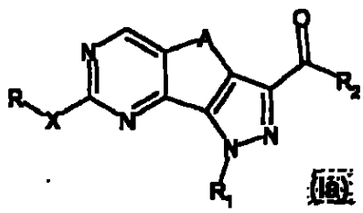
Step 2. (1S)-2-morpholin-4-yl-2-oxo-1-phenylethylamine hydrochloride

1.327 g of N-(tert-butoxycarbonyl)-(1S)-2-morpholin-4-yl-2-oxo-1-phenylethylamine was dissolved in 15 mL of dioxane and treated with 3.5 mL of HCl 4 M in dioxane overnight. The solvent was removed and the solid was triturated with diethylether yielding 920 mg of the product (yield 90%).

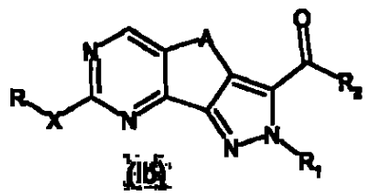
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.13 (m, 4 H) 3.54 (m, 4 H) 5.58 (m, 1 H) 7.50 (s, 5 H) 8.58 (s, 3 H).

CLAIMS

1) A pyrazolo-quinazoline derivative represented by formula (Ia) or (Ib)



(Ia)



(Ib)

wherein

R is hydrogen or an optionally substituted group selected from amino, straight or branched C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl;

X is a single bond or a divalent radical selected from -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- or $-SO_2-$, wherein R' is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R and R' may form a 5 to 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

R_1, bonded to any one of the nitrogen atoms of the pyrazole ring as per formulae (Ia) or (Ib), represents a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, in formula (Ib), R_1 is a divalent $-(CH_2)_n$-NH- group being linked to R_2, wherein n is 2 or 3;

R_2 is a group selected from -NR"R'", -N(OH)R", -OR" or -R", wherein R" and R'" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R" and R'" may form a 5 to 6 membered heteroaryl or heterocyclyl group, optionally containing one additional heteroatom selected among N, O or S;

A is a divalent group selected from $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ or -CH=CH-;

or a pharmaceutically acceptable salt thereof.

2) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group

-NH- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

3) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group -O- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

4) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group -S- and R_2 is a group selected from -NHR", -N(OH)R", -OR" or -R", wherein R" is an optionally substituted group selected from C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl; and R, R_1 and A are as above defined.

5) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group -NH- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

6) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group -O- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

7) A compound of formula (Ia) or (Ib), according to claim 1, wherein X is a group -S- and R_2 is a group -NHR" or -N(OH)R" wherein R" is a hydrogen atom or a straight or branched C_1-C_4 alkyl group; and wherein A, R and R_1 are as above defined.

8) A compound of formula (Ib), according to claim 1, wherein R, X and A are as above defined and R_1 and R_2 are linked together through a divalent $-(CH_2)_n$-NH- wherein n is as above defined.

9) A compound of formula (Ia) or (Ib) according to claim 1, wherein A is a group selected from $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$ or $-C(CH_3)_2-CH_2-$.

10) A compound of formula (Ia) or (Ib), according to claim 1, wherein any of the above R, R', R_1, R" and R"' group may be optionally substituted in any of their free positions by one or more groups independently selected from: halogen, nitro, oxo groups (=O), cyano, azido, alkyl, polyfluorinated alkyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, alkylaryl, alkylheterocyclyl, hydroxy, alkoxy, polyfluorinated alkoxy, aryloxy, arylalkyloxy, heterocyclyloxy, heterocyclylalkyloxy, methylenedioxy, alkylcarbonyloxy, alkylcarbonyloxyalkyl,

arylcarbonyloxy, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, aryloxycarbonyl, cycloalkyloxycarbonyl, amino, aminoalkyl, alkylaminoalkyl, alkylaminoalkyloxy, ureido, alkylamino, dialkylamino, arylamino, diarylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, alkoxycarbonylamino, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, alkylsulfonyl, arylsulfonyl, heterocyclylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylthio and alkylthio.

11) Any specific compound of formula (Ia) or (Ib), according to claim 1, optionally in the form of a pharmaceutically acceptable salt, among those defined in tables from VI to XXI.

12) A method for treating cell proliferative disorders caused by and/or associated with an altered protein kinase activity, by administering to a mammal in need thereof an effective amount of a pyrazolo-quinazoline derivative represented by formula (Ia) or (Ib) as set forth in claim 1.

13) The method acording to claim 12 wherein the protein kinase activity is Aurora 2 activity.

14) The method acording to claim 12 wherein the protein kinase activity is cell cycle dependent kinase activity.

15) The method according to claim 12 wherein the cell proliferative disorder is selected from the group consisting of cancer, Alzheimer's disease, viral infections, auto-immune diseases and neurodegenerative disorders.

16) The method according to claim 15 wherein the cancer is selected from the group consisting of carcinoma, squamous cell carcinoma, hematopoietic tumors of myeloid or lymphoid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

17) The method according to claim 12 wherein the cell proliferative disorder is selected from the group consisting of benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, psoriasis, vascular smooth cell proliferation associated

with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

18) The method according to claim 12 which provides tumor angiogenesis and metastasis inhibition as well as treatment of organ transplant rejection and host versus graft disease.

19) The method according to claim 12 which provides treatment or prevention of radiotherapy-induced or chemotherapy-induced alopecia.

20) The method according to claim 12 further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

21) The method according to claim 12 wherein the mammal in need thereof is a human.

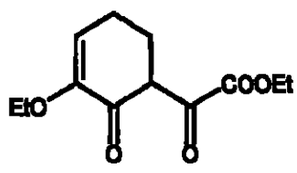
22) A method for inhibiting Aurora 2 kinase activity which comprises contacting the said kinase with an effective amount of a compound as defined in claim 1.

23) A method for inhibiting cyclin dependent kinase activity which comprises contacting the said kinases with an effective amount of a compound as defined in claim 1.

24) A process for preparing the compounds of formula (I), hence comprehensive of the compounds of formula (Ia) or (Ib) as defined in claim 1, or the pharmaceutically acceptable salts thereof, which process comprises:

(1) when A is a $-(CH_2)_2-$ group:

st.1) reacting 2-ethoxy-2-cyclohexen-1-one with diethyl oxalate, in the presence of lithium (bis-trimethylsilyl)amide [$LiN(TMS)_2$], so as to obtain a compound of formula (II)



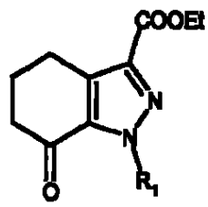
(II);

and treating it with a hydrazine derivative of formula (III)

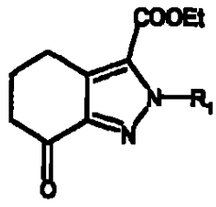
$$R_1\text{-}NHNH_2 \quad (III)$$

wherein R_1 is as above defined, according to the operative conditions set forth in any one of the steps (st.2a), (st.2b) or (st.2c)

st.2a) in the presence of a lower alcohol so as to obtain a mixture of the compounds of formula (IVa) and (IVb)



(IVa)



(IVb)

wherein R_1 is as above defined, and separating their mixture into the single compounds (IVa) and (IVb);

st.2b) in the presence of acetic acid so as to obtain a compound of formula (IVa);

st.2c) by alkylating a compound of formula (IVa) being obtained in step (st.2a) or (st.2b) and wherein R_1 is hydrogen with the compounds of formula (IVc)

$$R_1Y \quad (IVc)$$

wherein Y is a suitable leaving group selected from mesyl, tosyl or halogen, as to obtain a mixture of compounds of formula (IVa) and (IVb) wherein R_1 is as above defined and separating their mixture into the compounds (IVa) and (IVb);

st.3) reacting the compound of formula (IVa) prepared according to any one of steps (st.2a), (st.2b) or (st.2c), or of formula (IVb) prepared according to steps (st.2a) or (st.2c), with dimethylformamide-di-tert-butylacetale so as to obtain a compound of formula (Va) or (Vb)



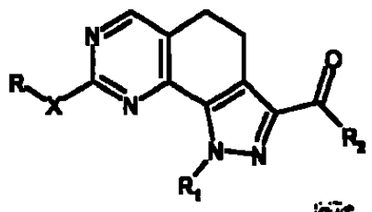
(Va)



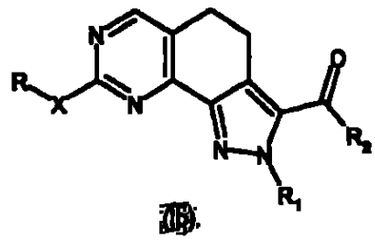
(Vb)

wherein R_1 is as above defined; and reacting the compound of formula (Va) or (Vb) according to any one of the alternative steps (st.4a), (st.4b) or (st.4c)

st.4a) with guanidine so as to obtain a compound of formula (Ia) or (Ib)



(Ia)



(Ib)

wherein R-X- is amino, R_2 is ethoxy, and R_1 is as above defined; and optionally converting them into other derivatives of formula (I);

st.4b) with a guanidine derivative of formula (VI)

$$R\text{-}NH\text{-}C(=NH)NH_2 \quad (VI)$$

wherein R is as above defined, so as to obtain a compound of formula (Ia) or (Ib) wherein R and R_1 are as above defined, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

st.4c) with an alkylisothiourea of formula (VII)

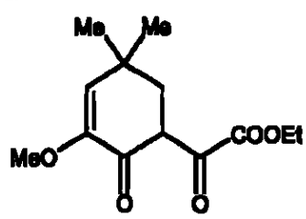
$$R\text{-}S\text{-}C(=NH)NH_2 \quad (VII)$$

wherein R is as above defined, so as to obtain a compound of formula (Ia) or (Ib) wherein R and R_1 are as above defined, X is -S- and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

st.4d) with methylisourea so as to obtain a compound of formula (Ia) or (Ib) wherein R_1 is as above defined, R is methyl, X is -O- and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

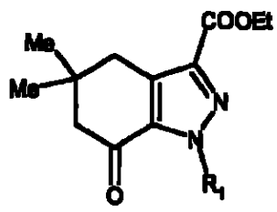
(2) when A is a $-C(CH_3)_2-CH_2-$ group:

st.5) reacting 2-methoxy-4,4-dimethyl-2-cyclohexen-1-one with diethyl oxalate, in the presence of $[LiN(TMS)_2]$, so as to obtain a compound of formula (VIII)

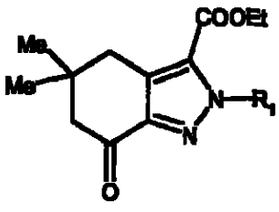


(VIII)

st.6) reacting the compound of formula (VIII) with a hydrazine derivative of formula (III) according to any one of previous steps (st.2a) or (st.2b) so as to obtain the compound of formula (IXa) or (IXb)



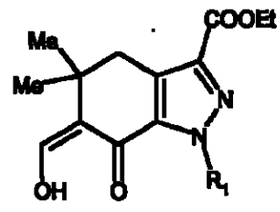
(IXa)



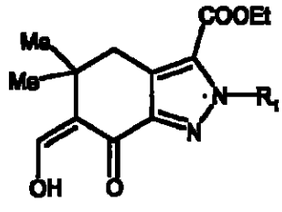
(IXb)

wherein R_1 is as above defined;

st.7) reacting the compound of formula (IXa) or (IXb) with ethyl formate under basic conditions, so as to obtain the compound of formula (Xa) or (Xb)

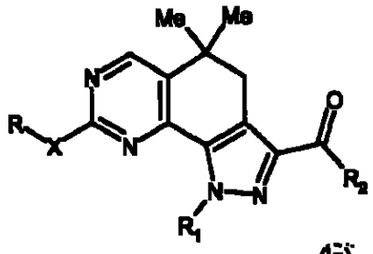


(Xa)

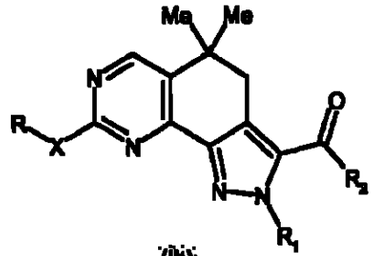


(Xb)

st.8) reacting the compound of formula (Xa) or (Xb) with a guanidine derivative of formula (VI), so as to obtain a compound of formula (Ia) or (Ib)



(Ia)

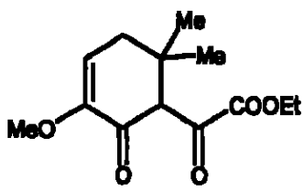


(Ib)

wherein R and R_1 are as above defined, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

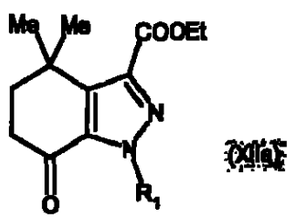
(3) when A is a $-CH_2-C(CH_3)_2-$ group:

st.9) reacting 2-methoxy-5,5-dimethyl-2-cyclohexen-1-one with diethyl oxalate in the presence of sodium hydride, so as to obtain the compound of formula (XI)

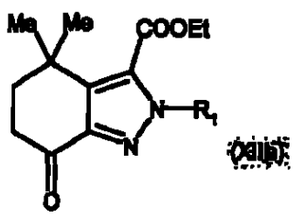


(XI)

st.10) reacting the compound of formula (XI) with a hydrazine derivative of formula (III) according to any one of previous steps (st.2a) or (st.2b) so as to obtain the compound of formula (XIIa) or (XIIb)



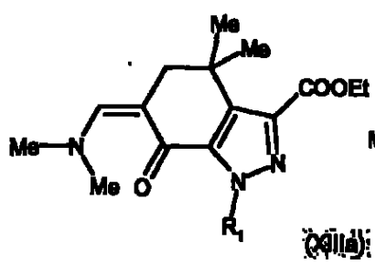
(XIIa)



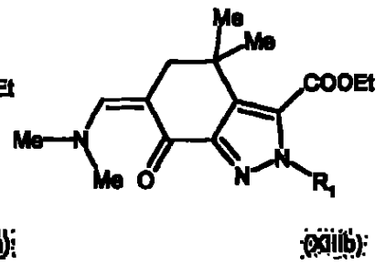
(XIIb)

wherein R_1 is as above defined;

st.11) reacting the compound of formula (XIIa) or (XIIb) with dimethylformamide-di-tert-butylacetale so as to obtain a compound of formula (XIIIa) or (XIIIb)

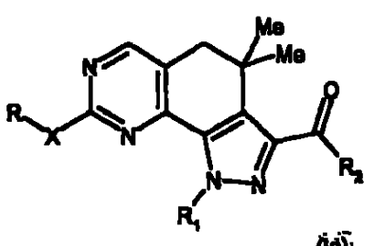


(XIIIa)

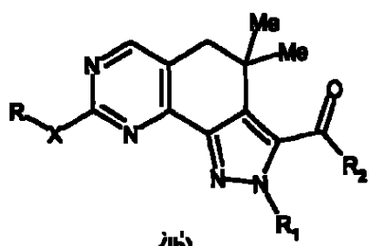


(XIIIb)

st.12) reacting the compound of formula (XIIIa) or (XIIIb) with a guanidine derivative of formula (VI), so as to obtain a compound of formula (Ia) or (Ib)



(Ia)

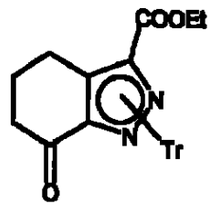


(Ib)

wherein R and R_1 are as above defined, X is -NH-, and R_2 is ethoxy; and optionally converting them into other derivatives of formula (I);

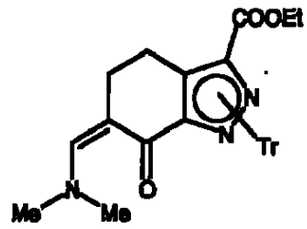
(4) when, in formula (Ib), R_1 is directly linked to R_2 so as to yield a tetra-cyclic ring structure:

st.13) reacting a compound of formula (IV) wherein R_1 is hydrogen, obtained according to (st.2) of the process, with triphenylmethyl chloride so as to obtain a compound of formula (XIV)

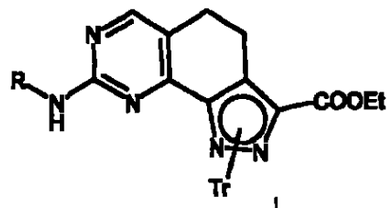


wherein Tr stands for trityl (triphenylmethyl);

st.14) reacting the compound of formula (XIV) with dimethylformamide-di-tert-butylacetale, as set forth in step (st.3), so as to obtain a compound of formula (XV)



st.15) reacting the compound of formula (XV) with a suitable guanidine derivative of formula (VI), as set forth in step (st.4b), so as to obtain a compound of formula (Ia) or (Ib)



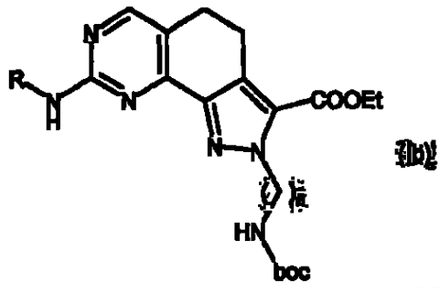
wherein R is as above defined, X is NH, R_1 is trityl and R_2 is ethoxy;

st.16) reacting the above compound of formula (Ia) or (Ib) under acidic conditions, so as to obtain the corresponding compound of formula (Ia) or (Ib) wherein R_1 is hydrogen;

st.17) reacting the above compound of formula (Ia) or (Ib) with a suitable alkylating agent of formula (XVI) in the presence of litium tert-butylate

$$Br\text{-}(CH_2)_n\text{-}NH\text{-}BOC \quad (XVI)$$

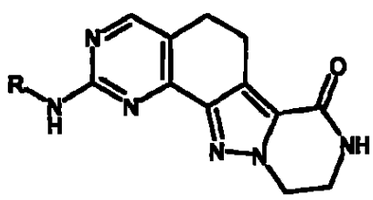
wherein n is 2 or 3, so as to obtain a compound of formula (Ib)



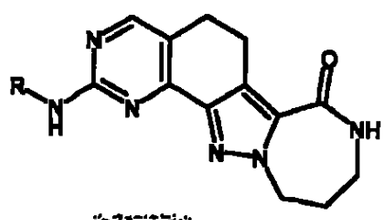
(Ib)

wherein n and R are as above defined;

st.18) reacting the above compound of formula (Ib) under acidic conditions, so as to convert the tert-butoxycarbonylamino group into amino (deprotection) and reacting it with cesium carbonate ($CsCO_3$) so as to obtain any one of the two compounds of formula (Ib)



(Id; n=2);

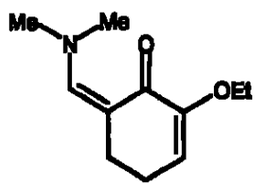


(Id; n=3);

wherein R is as above defined, and optionally converting them into other derivatives of formula (I);

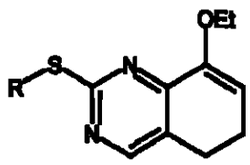
(5) when R_2 is a bulky group:

st.19) reacting 2-ethoxy-2-cyclohexenone with dimethylformamide-di-tert-butylacetale, as reported in step (st.3), so as to obtain a compound of formula (XVII)



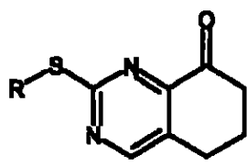
(XVII);

st.20) reacting the compound of formula (XVII) with a derivative of formula (VII), according to step (st.4c), so as to obtain a compound of formula (XVIII)



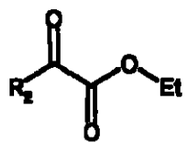
(XVIII)

wherein R is as above defined; and subsequently treating it under acidic conditions so as to obtain a compound of formula (XIX)



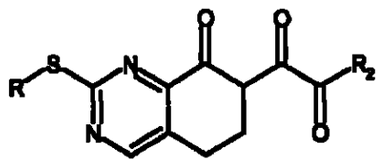
(XIX)

st.21) reacting the compound of formula (XIX) with a compound of formula (XX)



(XX)

wherein R_2 is a bulky group, so as to obtain a compound of formula (XXI)

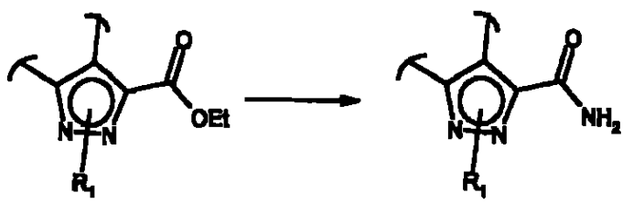


(XXI)

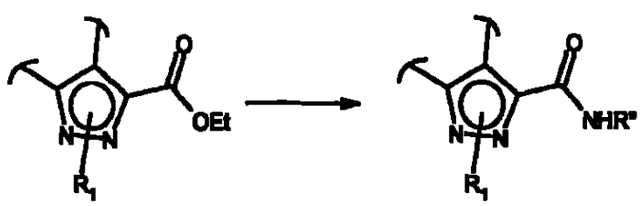
st.22) reacting the compound of formula (XXI) with a hydrazine derivative of formula (III), as per step (st.1) of the process, so as to obtain a compound of formula (I) wherein R and R_1 are as above defined, X is -S- and R_2 is a bulky group; and optionally converting them into other derivatives of formula (I).

25) The process of claim 24 wherein the compounds of formula (I) being obtained in any one of steps (st.4a), (st.4b), (st.4c), (st.8), (st.12), (st.13), (st.18) and (st.22), are converted into other compounds of formula (I), which process comprises converting those compounds of formula (I):

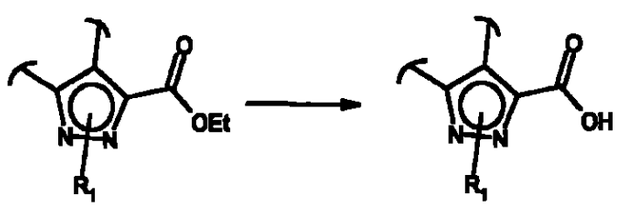
st.23) wherein R_2 is ethoxy into the compounds of formula (Ia) or (Ib) wherein R_2 is amino by treatment with ammonium hydroxide



st.24) wherein R_2 is ethoxy into the compounds of formula (I) wherein R_2 is a group -NHR", wherein R" is as above defined, by treatment with an amine of formula R"-NH_2 (XXII)



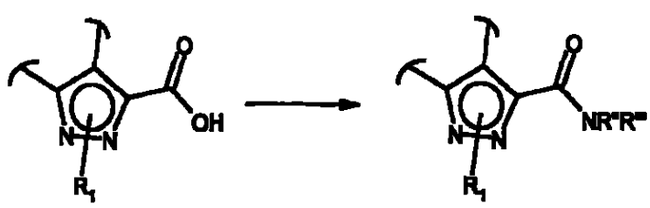
st.25) wherein R_2 is ethoxy into the compounds of formula (I) wherein R_2 is a group -OH through acidic or basic hydrolysis



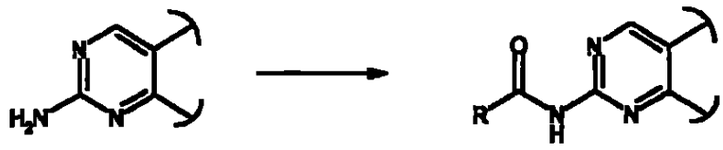
st.26) wherein R_2 is -OH into the compounds of formula (I) wherein R_2 is a group -NR"R'" or -N(OH)R" and R" and R'" are as above defined, through reaction with a derivative of formula (XXIII) or (XXIV)

R"R'"NH (XXIII) R"NHOH (XXIV)

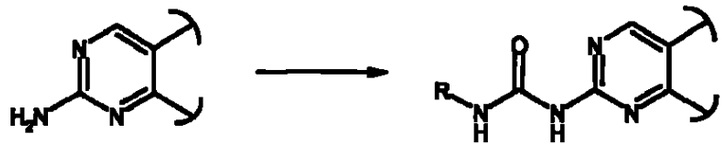
under basic conditions and in the presence of a suitable condensing agent



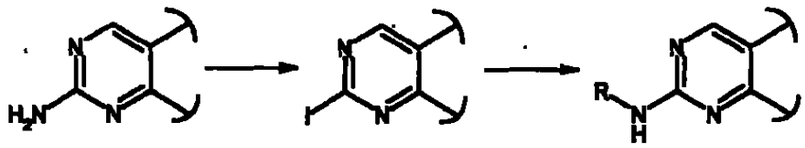
st.27) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is other than hydrogen as above defined, and X is -CONH-, through reaction with a compound of formula R-COCl (XXV)



st.28) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is other than hydrogen as above defined, and X is -NH-CO-NH-, through reaction with an isocyanate of formula R-NCO (XXVI)

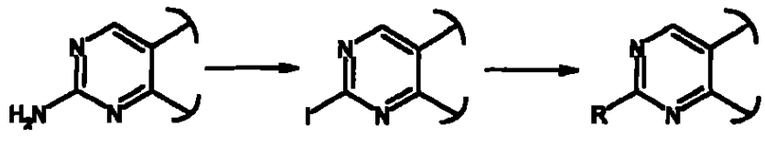


st.29) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is aryl and X is -NH-, by first converting the amino group to iodine with iso-amylnitrite and diiodomethane or cesium iodide, in the presence of iodine and CuI, and by subsequently reacting the iododerivative with an arylamine of formula R-NH_2 (XXVII), in the presence of palladium acetate and (2,2'-bis(diphenylphosphino))-1,1'-binaphthalene (BINAP)

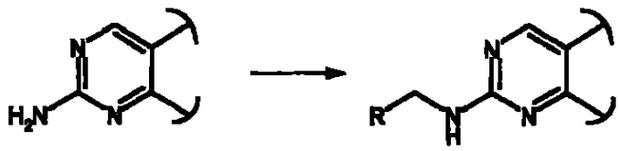


st.29a) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is alkyl, cycloalkyl, cycloalkyl-alkyl, arylalkyl, heterocyclyl, heterocyclylalkyl, and X is -NH-, by first converting the amino group to iodine, as described in the previous step (st.29), and by subsequently reacting the iododerivative with an alkyl, cycloalkyl, cycloalkyl-alkyl, arylalkyl, heterocyclyl or heterocyclylalkyl amine of formula RNH_2 (XXVII), wherein R is as therein defined;

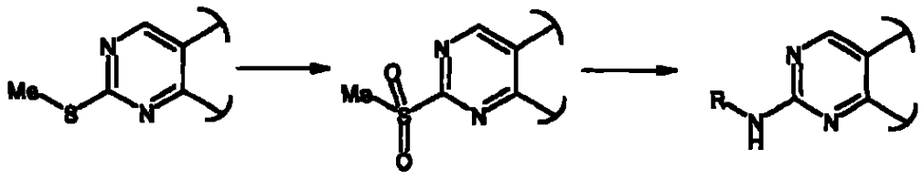
st.30) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is aryl and X is a single bond, by first converting the amino group to iodine, as per the above step (st.29), and by subsequently reacting the iododerivative with an arylboronic acid of formula R-$B(OH)_2$ (XXVIII), in the presence of a palladium derivative



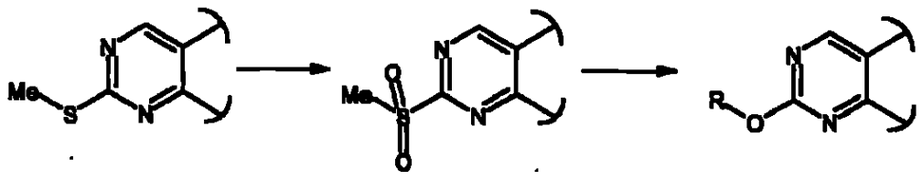
st.31) wherein R is hydrogen and X is -NH- into the compounds of formula (I) wherein R is arylmethyl and X is a single bond, by reaction with an aryl-aldehyde of formula R-CHO (XXIX) in the presence of sodium cyanoborohydride ($NaBH_3CN$)



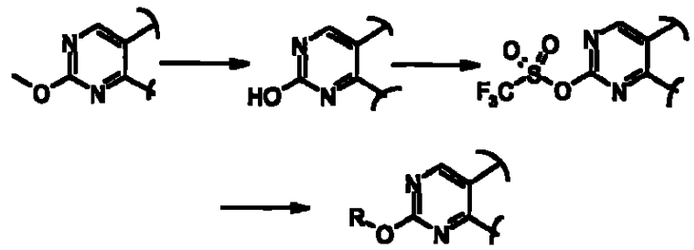
st.32) wherein R is methyl and X is -S- into the compounds of formula (I) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, arylalkyl or heterocyclylalkyl group, by first converting the RS- group into RSO_2- under oxidative conditions, and by then reacting the sulfonyl derivative with an amine of formula $R\text{-}NH_2$ (XXVII) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, arylalkyl or heterocyclylalkyl group



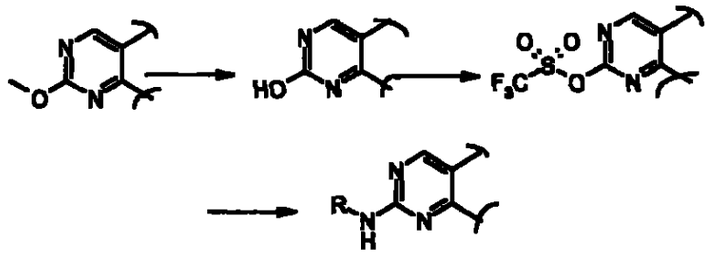
st.33) wherein R is methyl and X is -S- into the compounds of formula (I) wherein R is other than methyl and X is -O-, by first converting the RS- group into RSO_2- as per step (st.32) and by then reacting the sulfonyl derivative with a compound of formula R-OH (XXX)



st.33a) wherein R is methyl and X is -O- into the compounds of formula (I) wherein R is other than methyl and X is -O-, by first converting the MeO- group into HO-, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with a compound of formula R-OH (XXX)



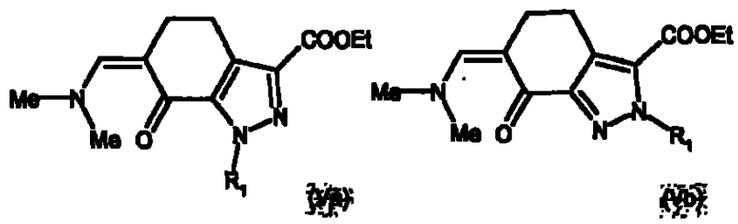
st.33b) wherein R is methyl and X is -O- may be converted into the compounds of formula (I) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkyl-alkyl, heterocyclylalkyl group, and X is -NH-, by first converting the MeO- group into HO-, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with an amine of formula R-NH_2 (XXVII) wherein R is an optionally substituted alkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, arylalkyl or heterocyclylalkyl group



st. 33c) wherein R is methyl and X is -O- may be converted into the compounds of formula (I) wherein R is an aryl and X is -NH-, by first converting the MeO- group into –OH, then by reacting it with a triflating agent so as to obtain the corresponding trifluoromethansulfonate and finally by reacting it with an amine of formula RNH_2 (XXVII) wherein R is an optionally substituted aryl in the presence of palladium acetate and BINAP;

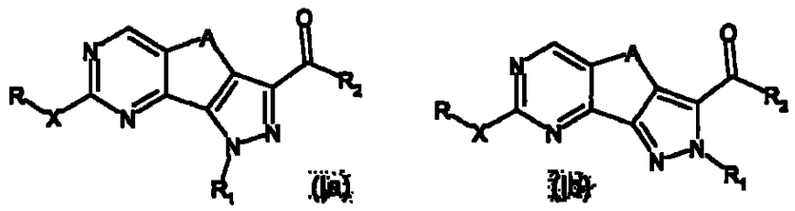
st.34) wherein A is a -$(CH_2)_2$- group may be converted into the compounds of formula (I) wherein A is a -CH=CH- group, under dehydrogenating operative conditions in the presence of a Pd or Pt catalyst.

26) A compound of formula (Va) or (Vb), as defined in step (st.3) of claim 24



wherein R_1 is a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl.

27) A library of two or more compounds of formula (Ia) or (Ib)



wherein

R is hydrogen or an optionally substituted group selected from amino, straight or branched C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl;

X is a single bond or a divalent radical selected from -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- or $-SO_2$-, wherein R' is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl or, together with the nitrogen atom to which they are bonded, R and R' may form a 5 to 6 membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

R_1, bonded to any one of the nitrogen atoms of the pyrazole ring as per formulae (Ia) or (Ib), represents a hydrogen atom or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, in formula (Ib), R_1 is a divalent $-(CH_2)_n$-NH- group being linked to R_2, wherein n is 2 or 3;

R_2 is a group selected from -NR"R'", -N(OH)R", -OR" or -R", wherein R" and R'" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or cycloalkyl-alkyl, aryl, arylalkyl, heterocyclyl or heterocyclylalkyl or, together with the nitrogen atom to which they are

bonded, R" and R"' may form a 5 to 6 membered heteroaryl or heterocyclyl group, optionally containing one additional heteroatom selected among N, O or S;

A is a divalent group selected from $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ or $-CH=CH-$;

or a pharmaceutically acceptable salt thereof.

28) A pharmaceutical composition comprising a therapeutically effective amount of a pyrazolo-quinazoline derivative of formula (Ia) or (Ib) as defined in claim 1, and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

29) A pharmaceutical composition according to claim 28 further comprising one or more chemotherapeutic agents.

30) A product or kit comprising a compound of formula (Ia) or (Ib) as defined in claim 1, or pharmaceutical compositions thereof as defined in claim 28, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

31) A compound of formula (Ia) or (Ib) as defined in claim 1 for use as a medicament.

32) Use of a compound of formula (Ia) or (Ib) as defined in claim 1 in the manufacture of a medicament with antitumor activity.

TÍTULO DE LA INVENCIÓN

DERIVADOS DE PIRAZOLO-QUINAZOLINA, PROCESO PARA SU PREPARACIÓN Y SU USO COMO INHIBIDORES DE QUINASA

ANTECEDENTE DE LA INVENCIÓN

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con derivados de pirazolo-quinazolina, con un proceso para su preparación, con composiciones farmacéuticas que las comprenden, y con su uso como agentes terapéuticos, particularmente en el tratamiento de cáncer y desórdenes de proliferación celular.

DISCUSIÓN DEL ANTECEDENTE

Varias drogas citotóxicas tales como, por ejemplo, fluorouracilo (5-FU), doxorubicina y camptotecinas, trayectorias metabólicas celulares afectadas o daño de ADN y el origen, en muchos casos, un bloqueo indirecto del ciclo celular. Por lo tanto, al producir un daño irreversible de las células tumorales y normales, estos agentes resultan en una toxicidad significativa y efectos colaterales.

A este respecto, se desean los compuestos capaces de funcionar como agentes antitumorales altamente específicos al conducir selectivamente a la detención de células tumorales y apoptosis, con eficacia comparable pero toxicidad reducida con relación a las drogas disponibles actualmente.

Es bien conocido que la progresión a través del ciclo celular se gobierna por una serie de controles de puntos de verificación, referidos de otra forma como puntos de restricción, que se regulan mediante una familia de enzimas conocidas como las quinasas dependientes de ciclina (cdk). En cambio, las cdks mismas se regulan en varios niveles tales como, por ejemplo, unión a ciclinas.

La activación coordinada e inactivación de diferentes complejos de ciclina/cdk es necesaria para la progresión normal a través del ciclo celular. Las transiciones G1-S y G2-M críticas se controlan mediante la activación de diferentes actividades de ciclina/cdk. En G1, la ciclina D/cdk4 y ciclina E/cdk2 se piensa median el ataque de la fase S. La progresión a través de la fase S requiere la actividad de la ciclina A/cdk2 mientras que la activación de la ciclina A/cdc2 (cdk1) y la ciclina B/cdc2 se requiere para el ataque de la mitosis. Para una referencia general a las ciclinas y las quinasas dependientes de ciclina ver, por ejemplo, Kevin

R. Webster et al, en Exp. Opin. Invest. Drugs, 1998, Vol. 7 (6), 865-887.

Los controles de punto de verificación son defectuosos en las células tumorales debido, en parte, a la desregulación de la actividad cdk. Por ejemplo, se ha observado en células tumorales la expresión alterada de la ciclina E y los cdks, y la supresión de la inhibición del gen inhibidor cdk p27 KIP en ratones ha mostrado que resulta en una incidencia más alta de cáncer.

La evidencia creciente apoya la idea de que los cdk son enzimas limitantes de la proporción en la progresión del ciclo celular y, como tales, representan objetivos moleculares para la intervención terapéutica. En particular, la inhibición directa de la actividad de quinasa cdk/ciclina debe ser de ayuda para restringir la proliferación no regulada de una célula tumoral.

Proteínas quinasa adicionales conocidas en la técnica por estar implicadas en el crecimiento de células cancerígenas son las quinasas Aurora, en particular la Aurora-2.

La Aurora-2 se encontró que estaba sobre expresada en un número d diferentes tipos de tumor. Sus mapas locus de gen en

el 20q13, una región cromosomal es frecuentemente amplificada en muchos cánceres, incluye el de seno [Cancer Res. 1999,59 (9) 2041-4] y el de colon.

La amplificación 20q13 se correlaciona con un pobre pronóstico en pacientes con cáncer de seno de nodo negativo y una expresión Aurora-2 incrementada es indicativa de un pobre pronóstico y un tiempo de supervivencia disminuido en pacientes con cáncer de vejiga [J. Natl. Cancer Inst., 2002,94 (17) 1320-9]. Para una referencia general al papel del Aurora-2 en la función de centrosoma anormal en cáncer ver también Molecular Cancer Therapeutics, 2003, 2, 589-595.

RESUMEN DE LA INVENCIÓN

Es un objeto de la invención suministrar compuestos que sean útiles para tratar desórdenes proliferativos celulares originados por y/o asociados con actividad de proteína quinasa alterada, por ejemplo actividad inhibitoria de Aurora-2 y actividad de quinasa dependiente del ciclo celular. Es otro objeto suministrar compuestos que tengan actividad inhibitoria de proteína quinasa.

La presente invención ha descubierto ahora que ciertas pirazolo-quinazolinas están involucradas con la actividad de

la proteína quinasa y son así útiles en terapia como agentes antitumorales y les falta, en términos tanto de toxicidad como de efectos colaterales, los inconvenientes anteriormente mencionados con drogas antitumorales habitualmente disponibles.

Más específicamente, las pirazolo-quinazolinas de la invención son útiles en el tratamiento de una variedad de cánceres que incluyen pero no están limitados a: carcinomas tal como el de vejiga, seno, colon, riñón, hígado, pulmón, que incluye cáncer de pulmón de célula pequeña, esófago, bilis-vejiga, ovario, páncreas, estómago, cerviz, tiroides, próstata, y piel, incluyendo carcinoma de célula escamoso; tumores hematopoyéticos de linaje linfoide incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de célula B, linfoma de célula T, linfoma Hodgkin, lilnfoma no Hodgkin, linfoma de célula vellosa y linfoma de Burkett; tumores hematopoyéticos de linaje mieloide, incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplásico y leucemia promielocítica; tumores de origen mesenquimal, incluyendo fibrosarcoma y rabdomiosarcoma; tumores del sistema nervioso central y periférico, incluyendo neuroblastoma astrocitoma, glioma y schwanomas; otros tumores, incluyendo melanoma, seminoma,

teratocarcinoma, osteosarcoma, xeroderma pigmentoso, queratoxantoma, cáncer folicular tiroides y sarcoma Kaposi.

Debido al papel clave de las quinasas de ciclo celular tal como Aurora o cdk en la regulación de la proliferación celular, estos derivados de pirazolo-quinazolina son también útiles en el tratamiento de una variedad de desórdenes proliferativos de células tal como, por ejemplo, hiperplasia benigna de próstata, adenomatosis familiar, poliposis, neurofibromatosis, soriasis, proliferación de célula lisa vascular asociada con ateroesclerosis, fibrosis pulmonar, artritis, glomerulonefritis y estenosis y restenosis post-quirúrgica.

Los compuestos de la invención pueden ser útiles en el tratamiento de enfermedad de Alzheimer, como se sugirió por el hecho de que el cdk5 esté involucrado en la fosforilación de la proteína tau (J. Biochem. 117, 741-749, 1995).

Los compuestos de esta invención, como moduladores de apoptosis, pueden ser también útiles en el tratamiento de cáncer, infecciones virales, prevención del desarrollo de SIDA en individuos infectados VIH, enfermedades autoinmunes y desórdenes neurodegenerativos.

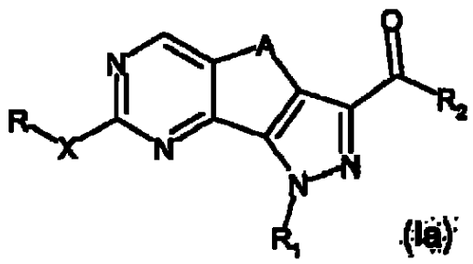
Los compuestos de la invención pueden ser útiles para inhibir la angiogénesis tumoral y la metástasis, así como también el tratamiento de rechazo por transplante de órgano y enfermedad de huésped versus injerto.

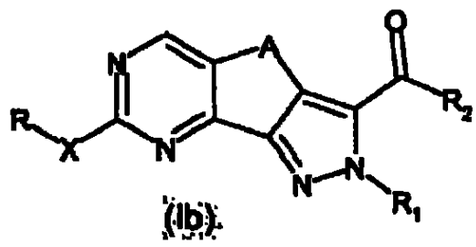
Los compuestos de la invención también pueden actuar como inhibidores de otras proteínas quinasas, por ejemplo, la proteína quinasa C en diferentes isoformas, Met, PAK-4, PAK-5, ZC-1, STLK-2, DDR-2, Bub-1, PLK, Chk1, Chk2, HER2, raf1, MEK1, MAPK, EGF-R, PDGF-R, FGF-R, IGF-R, PI3K, quinasa weel, Src, Abl, Akt, MAPK, ILK, MK-2, IKK-2, Cdc7, Nek, y así ser efectivos en el tratamiento de enfermedades asociadas con otras proteínas quinasa.

Los compuestos de la invención también son útiles en el tratamiento y prevención de alopecia inducida por radioterapia o quimioterapia.

De acuerdo con esto, en una primera modalidad, la presente invención suministra un método para tratar desórdenes proliferativos de células originados por y/o asociados con actividad de proteína quinasa alterada, como por ejemplo la actividad de Aurora-2 y actividad de quinasa dependiente del ciclo celular, al administrar a un mamífero necesitado de

éste una cantidad efectiva de derivados de pirazolo-quinazolina representados por la fórmula (Ia) o (Ib)


(Ia)


(Ib)

En donde R es hidrógeno o un grupo opcionalmente sustituido seleccionado de amino, alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_{10}, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo;

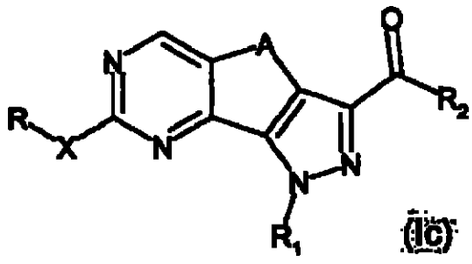
X es un enlace simple o un radical divalente seleccionado de -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- o $-SO_2-$, en donde R' es hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R y R' pueden formar un grupo heteroarilo o heterociclilo de 5 a 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

R_1, unido a uno cualquiera de los átomos de nitrógeno del anillo de pirazolo como por las fórmulas (Ia) o (Ib), representa un átomo de hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, en la fórmula (Ib), R_1 es un grupo divalente $-(CH_2)_n-NH-$ que está ligado a R_2 en donde n es 2 o 3;

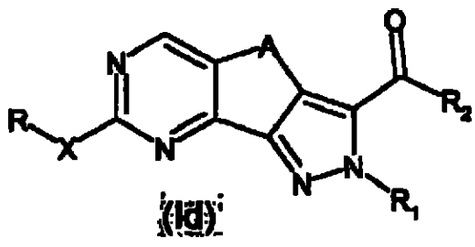
R_2 es un grupo seleccionado de -NR''R''',-N(OH)R'',-OR'' o -R'', en donde R'' y R''' son, cada uno independientemente, hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R'' y R''' pueden formar un grupo heteroarilo o heterociclilo de 5 o 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

A es un grupo divalente seleccionado de $-CH_2-$, $-(CH_2)_2-$,$-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ o -CH=CH-; o una sal farmacéuticamente aceptable de estos.

En otra modalidad, la presente invención suministra un método para tratar desórdenes proliferativos de células originados y/o asociados con actividad de proteína quinasa alterada, actividad de quinasa dependiente del ciclo celular, al administrar a un mamífero necesitado de ello una cantidad efectiva de un derivado de pirazolo-quinazolina representado por la fórmula anterior (Ia) o (Ib).



(Ic)



(Id)

En una modalidad preferida de los métodos descritos anteriormente, el desorden proliferativo de las células se selecciona del grupo que consiste de cáncer, enfermedad de Alzheimer, infecciones virales, enfermedades autoinmunes y desórdenes neurodegenerativos.

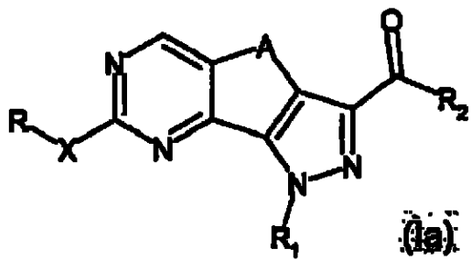
Los tipos específicos de cáncer que pueden ser tratados incluyen carcinoma, carcinoma de célula escamosa, tumores hematopoyéticos de linaje mieloide o linfoide, tumores de origen mesenquimal, tumores del sistema nervioso central y periférico, melanoma, seminoma, teratocarcinoma,

osteosarcoma, xeroderma pigmentoso, queratoxantoma, cáncer folicular tiroides, y sarcoma Kaposi.

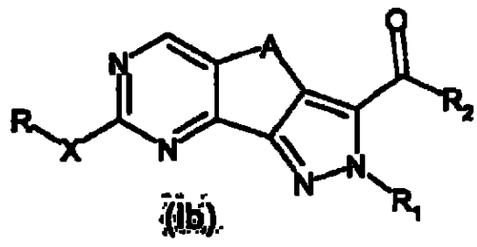
En otra modalidad preferida del método descrito anteriormente, el desorden proliferativo celular se selecciona del grupo que consiste de hiperplasia benigna de próstata, adenomatosis familiar, poliposis, neurofibromatosis, soriasis, proliferación de célula lisa vascular asociada con ateroesclerosis, fibrosis pulmonar, artritis, glomerulonefritis y estenosis y restenosis post-quirúrgica. Además, el método de la invención suministra angiogénesis tumoral e inhibición de metástasis así como también tratamiento de rechazo de transplante de órgano y enfermedad de huésped versus injerto. Los métodos de la invención también suministran inhibición del ciclo celular o inhibición dependiente de cdk/ciclina.

Además de lo anterior, los métodos objeto de la presente invención suministran tratamiento y prevención de alopecia inducida por radioterapia o por quimioterapia.

La presente invención suministra derivados de pirazolo-quinazolina representados por la fórmula (Ia) o (Ib)



(Ia)



(Ib)

En donde R es hidrógeno o un grupo opcionalmente sustituido seleccionado de amino, alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_{10}, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo;

X es un enlace simple o un radical divalente seleccionado de -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- o $-SO_2-$, en donde R' es hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R y R' pueden formar un grupo heteroarilo o heterociclilo de 5 a 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

R_1, unido a uno cualquiera de los átomos de nitrógeno del anillo de pirazolo como por las fórmulas (Ia) o (Ib), representa un átomo de hidrógeno o un grupo opcionalmente

sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, en la fórmula (Ib), R_1 es un grupo divalente $-(CH_2)_n-NH-$ que está ligado a R_2, en donde n es 2 o 3;

R_2 es un grupo seleccionado de -NR''R''',-N(OH)R'',-OR'' o -R'', en donde R'' y R''' son, cada uno independientemente, hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R'' y R''' pueden formar un grupo heteroarilo o heterociclilo de 5 o 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

A es un grupo divalente seleccionado de $-CH_2-$, $-(CH_2)_2-$,$-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ o -CH=CH-; o una sal farmacéuticamente aceptable de estos.

La presente invención también incluye métodos para sintetizar los derivados de pirazolo-quinazolina representados por la fórmula (Ia) o (Ib) que, a menos que se establezca otra cosa, puede estar convenientemente agrupado y definido como los

compuestos fórmula (I). Las composiciones farmacéuticas que comprenden los derivados pirazolo-quinazolina de la fórmula (I) también están incluidos en la presente invención.

Una apreciación más completa de la invención y muchas de las ventajas relacionadas con ésta serán fácilmente obtenidas en la medida en que se entiende mejor mediante referencia a la siguiente descripción detallada.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Varios compuestos heterocíclicos son conocidos en la técnica como inhibidores de proteína quinasa. Como un ejemplo, 2-carboxamido-pirazoles y 2-ureido-pirazoles, y derivados de estos, han sido descritos como inhibidores de proteína quinasa en las solicitudes de patente internacional WO 01/12189, WO 01/12188, WO 02/48114 y WO 02/70515, todas a nombre del mismo solicitante.

Los compuestos bicíclicos fusionados que comprenden porciones de pirazolo y que poseen actividad inhibitoria de quinasa también han sido descritos en la WO 00/69846, WO 02/12242 así como también WO 03/028720 y aún la solicitud de patente US no publicada 60/381092 (presentada en Mayo 17, 2002), todas a nombre del mismo solicitante.

Los derivados tricíclicos fusionados que poseen actividad inhibitoria de quinasa también son descritos en dos solicitudes copendientes PCT/EP03/01594 y PCT/US03/04844 (ambas reivindicando prioridad de Febrero 19, 2002 de las solicitudes US No. 60/357918 y No. 60/357960, respectivamente) y con este incorporado como referencia; ninguna de dichas aplicaciones describe específicamente los derivados en referencia.

Además, los derivados de pirimidina policíclica fusionada como inhibidor de proteína quinasa también son descritos en la solicitud de patente internacional WO 98/58926 y WO 98/28281, ambas a nombre de CellTech Therapeutics Ltd; aunque comprendidos dentro de la fórmula general de ambas solicitudes, ningún ejemplo específicode pirazolo-quinazolinas de la presente invención se ejemplifica allí.

Finalmente, los derivados de pirimidina fusionada con anillo heterocíclico para el tratamiento de enfermedades hiperproliferativas se describen en la WO 96/40142 a nombre de Pfizer Inc.

Los compuestos de fórmula (I) de la invención pueden tener átomos de carbono asimétrico y pueden por lo tanto existir

como isómeros ópticos individuales, como mezclas racémicas o como cualquier otra mezcla que comprende una mayoría de uno o dos isómeros ópticos, los cuales pretenden todos estar dentro del alcance de la presente invención.

De manera similar, el uso de un agente antitumoral de todos los isómeros posibles y sus mezclas y tanto los metabolitos como los bio-precursores farmacéuticamente aceptables (denominados de otra forma como pro-drogas) de los compuestos de fórmula (I) también están dentro del alcance de la presente invención.

Las prodrogas son cualesquier compuestos covalentemente unidos que liberan la droga padre activa, de acuerdo con la fórmula (I), invivo.

En los casos cuando los compuestos pueden existir en formas tautoméricas, por ejemplo tautómeros de queto-enol, cada forma tautomérica se contempla como estando incluida dentro de esta invención sea que exista en equilibrio o predominantemente en una forma.

En la presente descripción, a menos que se especifique otra cosa, con el término alquilo C_1-C_6 recto o ramificado, nosotros pretendemos cualquiera de los grupos tales como, por

ejemplo, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, terc-butilo, sec-butilo, n-pentilo, n-hexilo, y similares.

Con el término cicloalquilo C_3-C_{10} nosotros pretendemos, a menos que se especifique otra cosa, un anillo cicloalifático tal como ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo, así como también cualquier grupo cicloalquilo puenteado hasta con 10 átomos de carbono.

El término arilo incluye hidrocarburos carbocíclicos o heterocíclicos con desde 1 a 2 porciones de anillo, sea fusionados o ligados uno al otro mediante enlaces sencillos, en donde al menos uno de los anillos es aromático; si está presente, cualquier hidrocarburo heterocíclico aromático también se refiere como grupo heteroarilo, que comprende un anillo de 5 o 6 miembros con desde 1 a 3 heteroátomos seleccionados de N, O o S.

Ejemplos de grupos arilo de acuerdo con la invención son, por ejemplo, fenilo, bifenilo, α- o β-naftilo, dihidronaftilo, tienilo, benzotienilo, furilo, benzofuranilo, pirrolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxazolilo, isoxazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, indolilo, isoindolilo, purinilo, quinolilo,

isoquinolilo, dihidroquinolinilo, quinoxalinilo, benzodioxolilo, indanilo, indenilo, triazolilo, y similares. A menos que se especifique otra cosa, el término heterociclilo incluye heterociclos saturados, parcialmente insaturados o completamente insaturados de 5 o 6 miembros con desde 1 a 3 heteroátomos seleccionados entre N, O o S. Aparte de los heterociclos completamente insaturados, previamente referidos como heterociclos aromáticos y comprendidos por el término arilo, ejemplos de heterociclos saturados o parcialmente insaturados de acuerdo con la invención son, por ejemplo, pirano, pirrolidina, pirrolino, imidazolino, imidazolidino, pirazolidino, pirazolino, tiazolilo, tiazolidino, dihidrofurano, tetrahidrofurano, 1,3-dioxolano, piperidino, piperazino, morfolino y similares.

De todos los anteriores, es claro para el experto que cualquier compuesto de la invención en donde X representa un enlace sencillo tiene que estar destinado a tener un grupo R directamente ligado a la porción pirimidina.

De acuerdo con los significados de sustituyente anteriormente indicados y a menos que se especifique otra cosa, cualquiera de los grupos anteriores R, R', R1, R'' y R''' puede ser opcionalmente sustituido en cualquiera de sus posiciones libres por uno o más grupos, por ejemplo 1 a 6 grupos,

independientemente seleccionado de: halógeno, nitro, grupos oxo (=O), ciano, azido, alquilo, alquilo polifluorinado, hidroxialquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, cicloalquilo, alquilarilo, alquilheterociclilo, hidroxi, alcoxi, alcoxi polifluorinado, ariloxi, arilalquiloxi, heterocicliloxi, heterociclilalquiloxi, metilenodioxi, alquilcarboniloxi, alquilcarboniloxialquilo, arilcarboniloxi, carboxi, alcoxicarbonilo, alcoxicarbonilalquilo, ariloxicarbonilo, cicloalquiloxicarbonilo, amino, aminoalquilo, alquilaminoalquilo, alquilaminoalquiloxi, ureido, alquilamino, dialquilamino, arilamino, diarilamino, formilamino, alquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, alcoxicarbonilamino, alcoxiimino, alquilsulfonilamino, arilsulfonilamino, formilo, alquilcarbonilo, arilcarbonilo, heterociclilcarbonilo, cicloalquilcarbonilo, heterociclilcarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, arilaminocarbonilo, alquilsulfonilo, arilsulfonilo, heterociclilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, ariltio y alquiltio.

A este respecto, con el término átomo halógeno nosotros significamos un átomo de flúor, cloro, bromo o yodo.

Con el término alquilo perfluorinado nosotros significamos cualquiera de los grupos alquilo C_1-C_6 rectos o ramificados que son sustituidos por más de un átomo de flúor tal como, por ejemplo, trifluorometilo, trifluoroetilo, 1,1,1,3,3,3-hexafluoropropilo, y similares.

Con el término alcoxi, ariloxi, heterocicliloxi y derivados de estos, por ejemplo, alcoxi perfluorinado, nosotros pretendemos cualquiera de los grupos alquilo, arilo o heterociclilo anteriores ligados al resto de la molécula a través de un átomo de oxígeno (-O-).

De todos los anteriores, es claro para la persona experta que cualquier grupo cuyo nombre sea un nombre compuesto tal como, por ejemplo, arilalquilo o heterociclilalquilo tiene que ser convencionalmente construido por las partes de las cuales este se deriva, por ejemplo, mediante un grupo alquilo que es adicionalmente sustituido por arilo o heterociclilo, en donde alquilo, arilo o heterociclilo son como se definió anteriormente.

De manera similar, cualquiera de los términos tales como, por ejemplo, alquiltio, alquilamino, dialquilamino, alcoxicarbonilo, alcoxicarbonilamino, heterociclilcarbonilo, heterociclilcarbonilamino, cicloalquiloxicarbonil y

similares, incluyen grupos en donde las porciones alquilo, alcoxi, arilo, cicloalquilo y heterociclilo son como se definió anteriormente.

Las sales farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen las sales de adición de ácido con ácido inorgánicos u orgánicos, por ejemplo, ácido nítrico, clorhídrico, bromhídrico, sulfúrico, perclórico, fosfórico, acético, trifluoacético, propiónico, glicólico, láctico, oxálico, malónico, málico, maléico, ttartárico, cítrico, benzoico, cinámico, mandélico, metanosulfónico, isetiónico y salisílico, así como también las sales con las bases inorgánicas u orgánicas, por ejemplo, los metales alcalinos o alcalino térreos, hidróxidos de sodio, potasio, calcio o magnesio, carbonatos o bicarbonatos, aminas acíclicas o cíclicas, preferiblemente metilamina, etilamina, dietilamina, trietilamina, piperidina y similares.

De acuerdo con una primera modalidad de la invención dirigida a los compuestos de fórmula (Ia) o (Ib), los derivados preferidos son aquellos en donde X es un grupo -NH- y R_2 es un grupo seleccionado de -NHR'', -N(OH)R'', -OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado de cicloalquilo C_3-C_6 o cicloalquil-alquilo, arilo,

arilalquilo, heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

También preferidos son los compuestos de fórmula (Ia) o (Ib) en donde X es un grupo -O- y R_2 es un grupo seleccionado de -NHR'',-N(OH)R'', -OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado de cicloalquilo C_3-C_6 o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

También preferidos son los compuestos de fórmula (Ia) o (Ib) en donde X es un grupo -S- y R_2 es un grupo seleccionado de -NHR'', -N(OH)R'', -OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado de cicloalquilo C_3-C_6 o cicloalquil cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

Aún más preferido, dentro de los anteriores casos de compuestos (Ia) o (Ib) están aquellos mismos derivados en donde A es un grupo $-(CH_2)_2-$.

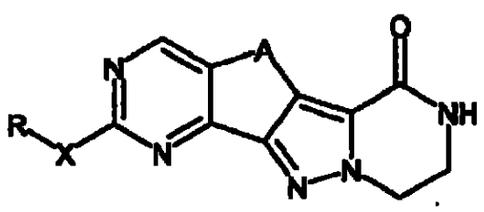
De acuerdo con otra modalidad de la invención dirigida a los compuestos de la fórmula (Ia) o (Ib), una clase de compuestos

preferidos se representa por aquellos derivados en donde X es un grupo NH-y R_2 es un grupo -NHR" o -N(OH)R" en donde R" es un átomo de hidrogeno o un grupo alquilo C_1-C_4 recto o ramificado, en donde A, R y R_1 son como se definió anteriormente.

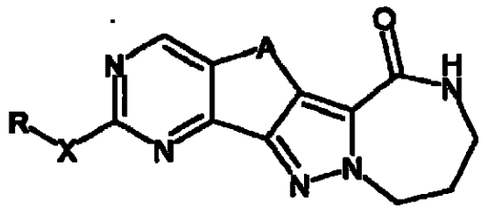
Otra clase de compuestos preferidos de la invención de fórmula (Ia) o (Ib) se representa por los derivados en donde X es un grupo -O- y R_2 es un grupo -NHR" o -N(OH)R" en donde R" es un átomo de hidrógeno o un grupo alquilo recto o ramificado C_1-C_4; y en donde A, R y R_1 son como se definió anteriormente.

Otra clase de compuestos preferidos de la invención de fórmula (Ia) o (Ib) se representa por los derivados donde X es un grupo -S- y R_2 es un grupo -NHR" o -N(OH)R" en donde R" es un átomo de hidrógeno o un grupo alquilo recto o ramificado C_1-C_4; y en donde A, R y R_1 son como se definió anteriormente.

Otra clase de compuestos preferidos de la invención de fórmula (Ib) se representan mediante los derivados en donde R, X y A son como se definió anteriormente y R_1 y R_2 están ligados juntos a través de un grupo divalente $-(CH_2)_n$-NH- con el fin de dar origen a:



n=2



n=3

También preferidas dentro de la clase anterior de derivados de fórmula (IA) y (IB), están los compuestos en donde A es un grupo seleccionado de $-CH_2-C(CH_3)_2-$ o $-C(CH_3)_2-CH_2-$.

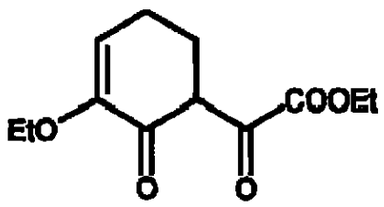
Para una referencia a cualquier compuesto específico de fórmula (IA) y (IB) de la invención, opcionalmente en la forma de una sal farmacéuticamente aceptable, ver la sección experimental y las reivindicaciones.

Como de indicó anteriormente, un objeto adicional de la presente invención se representa mediante un proceso para preparar los compuestos de fórmula (I) cuya fórmula, a menos que se especifique otra cosa, esta tiene que estar destinada a comprender los derivados de la fórmula (IA) y (IB).

Por la tanto los compuestos de fórmula (I) o la sal farmacéuticamente aceptable de estos se puede obtener mediante un proceso que comprende:

(1) cuando A es un grupo $-(CH_2)-$:

et. 1) hace reaccionar 2-etoxi-2-ciclohexen-1-ona con dietiloxolato, de la presencia de litio (bis-trimetilsilil) amida [LiN(TMS)2], con el fin de obtener un compuesto de fórmula (II)



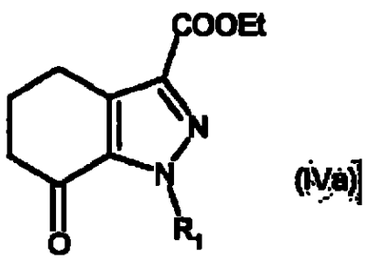
(II)

y tratarlo con un derivado de hidrazina de la fórmula (III)

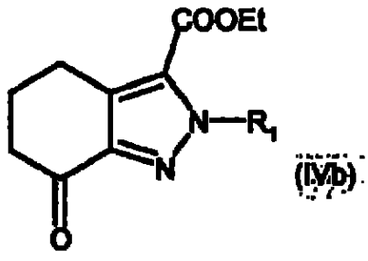
$$R_1\text{-}NHNH_2 \quad (III)$$

En donde R_1 tiene los significados anteriormente reportados, de acuerdo a las condiciones operativas establecidas en cualquiera de las etapas (et. 2a), (et. 2b) o (et. 2c)

et. 2a) en la presencia de un alcohol inferior con el fin de obtener un mezcla de los compuestos de fórmula (IVa) y (IVb)



(IVa)



(IVb)

En donde R_1 es como se reportó anteriormente, y separar su mezcla en los compuestos simples, (IVa) y (IVb);

et. 2b) en la presencia de acido acético con el fin de obtener un compuesto de fórmula (IVa);

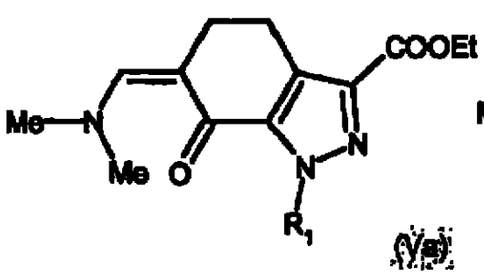
et. 2c) al aquilatar un compuesto de fórmula (IVa) que es obtenido en la etapa (et. 2a) o (et. 2b) y en donde R_1 es hidrógeno con los compuestos de fórmula (IVc)

R1Y (IVc)

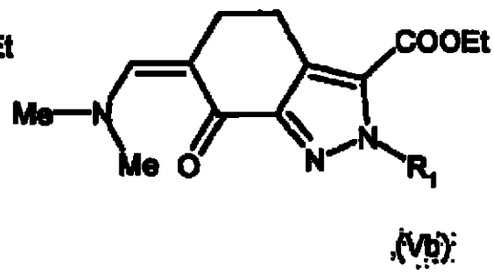
En donde Y es un grupo saliente adecuado como mesilo, tosilo, halógeno con el fin de obtener una mezcla de compuestos fórmula (IVa) y (IVb) en donde R_1 es como se definió anteriormente y separar su mezcla en los compuestos (IVa) y (IVb);

et.3) hacer reaccionar el compuesto de fórmula (IVa) preparado de acuerdo con una cualquiera de las etapas

(et.2a), (et.2b) o (et.2c), o de fórmula(IVb) preparado de acuerdo con las etapas (et.2a) o (et.2c), con dimetilformamida-di-terc-butilacetal para obtener un compuesto de fórmula (Va) o (Vb).

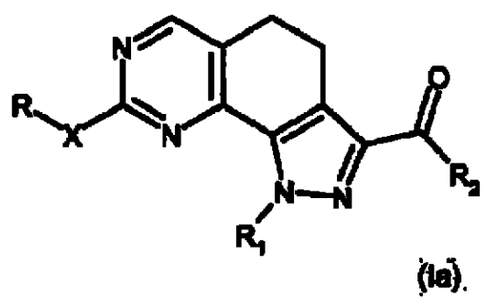


(Va)

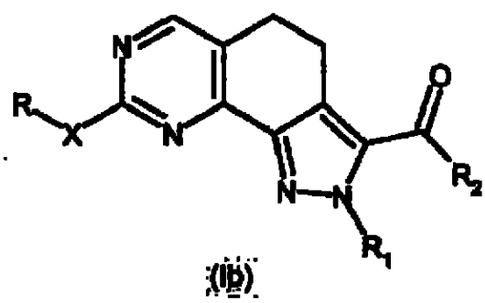


(Vb)

En donde R_1 escomo se reportó anteriormente; y hacer reaccionar el compuesto de fórmula (Va) o (Vb) de acuerdo una cualquiera de las etapas alternativas (et. 4a), (et. 4b) o (et. 4c) et. 4a) con guanidina con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

Donde R-X-es amino, R_2 es etoxi, y R_1 es como se definió anteriormente; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4b) con un derivado de guanidina de fórmula (VI)

R-NH-C (--NH) NH2 (VI)

donde R es como se reportó anteriormente con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R y R_1 son como se reportó anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4c) con una alquilisotiourea de fórmula (VII)

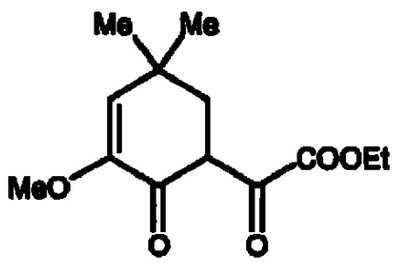
R-S-C(=NH)NH_2 (VII)

Donde R es como se reportó anteriormente con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R y R_1 son como se reportó anteriormente, X es -S- y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4d) con metilisourea con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R_1 es como se reportó anteriormente R es metilo, X es -O- y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

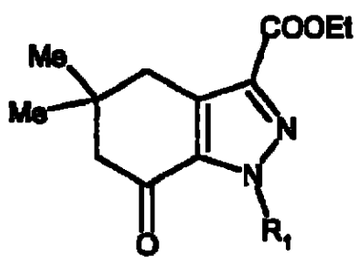
(2) en donde A es un grupo $-C(CH_3)_2-CH_2-$:

et. 5) hacer reaccionar 2-metoxi-4,4-dimetil-2-ciclohexen-1-ona con dietil oxalato, en la presencia de $[LiN(TMS)_2]$, con el fin de obtener un compuesto de fórmula (VIII)

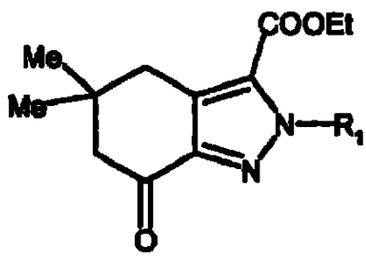


(VIII)

et. 6) hacer reaccionar el compuesto de fórmula (VIII) con un derivado de hidrazina de fórmula (III) de acuerdo a una cualquiera de las etapas previas (et. 2a) o (et. 2b) con el fin de obtener un compuesto de fórmula (IXa) o (IXb)



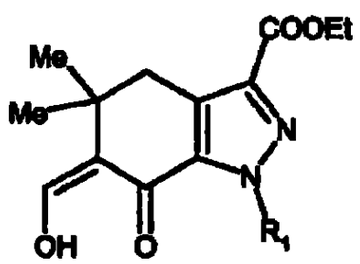
(IXa)



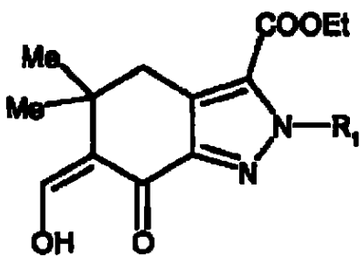
(IXb);

en donde R_1 es como se reportó anteriormente;

et. 7) hacer reaccionar el compuesto de fórmula (IXa) o (IXb) con formato de etilo en condiciones básicas con el fin de obtener un compuesto de fórmula (Xa) o (Xb)

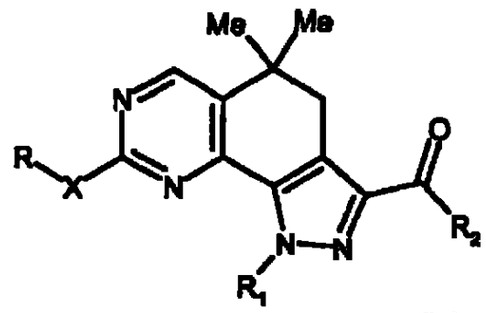


(Xa)

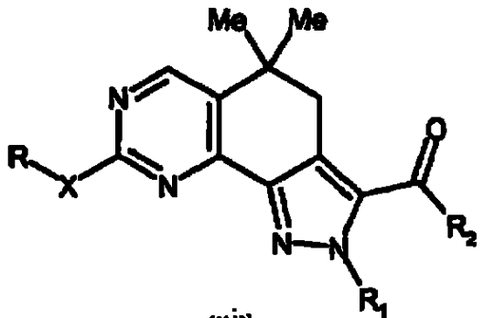


(Xb)

et. 8) hacer reaccionar el compuesto de fórmula (Xa) o (Xb) con guanidina o un derivado de guanidina de fórmula (VI), con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



(Ia)

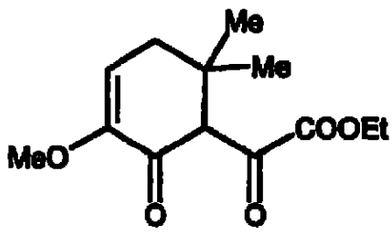


(Ib)

en donde R y R_1 son como se reportó anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

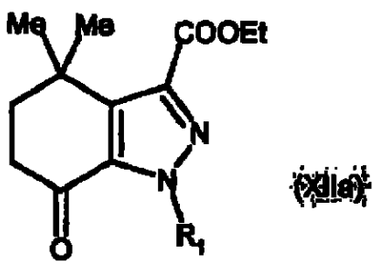
(3) cuando A es un grupo $-CH_2-C(CH_3)_2-$:

et. 9) hacer reaccionar 2-metoxi-5,5-dimetil-2-ciclohexen-1-ona con dietil oxalato en la presencia de hidruro de sodio, con el fin de obtener un compuesto de fórmula (XI)

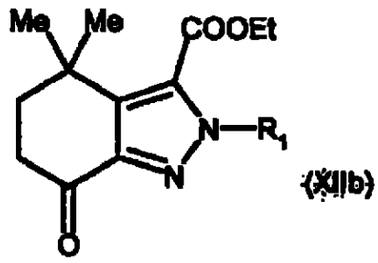


(XI)

et. 10) hacer reaccionar un compuesto de fórmula (XI) con derivado de hidrazina de fórmula (III) de acuerdo a una cualquiera de las etapas (et. 2a) o (et. 2b) con el fin de obtener un compuesto de fórmula (XI o (XIIb)



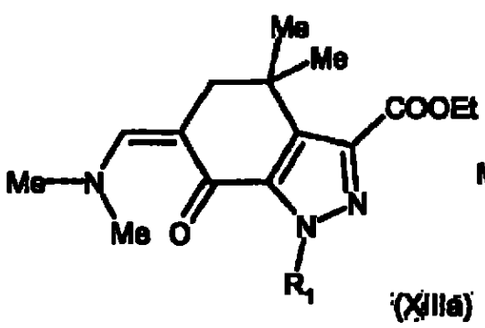
(XIIa)



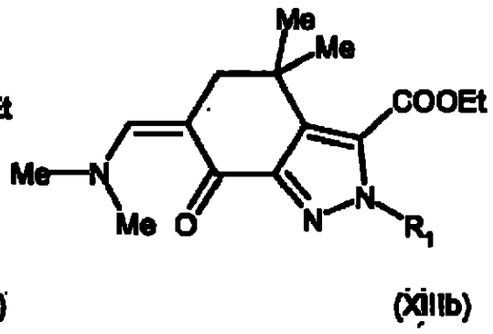
(XIIb)

en donde R_1 como se reportó anteriormente;

et. 11) hacer reaccionar el compuesto de fórmula (XIIa) o (XIIb) con dimetilformamida-di-terc-butilacetalo con el fin de obtener un compuesto de fórmula (XIIIa) o (XIIIb)

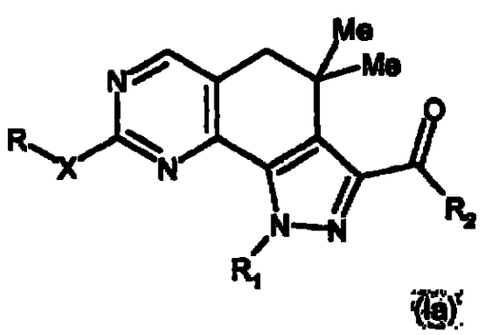


(XIIIa)

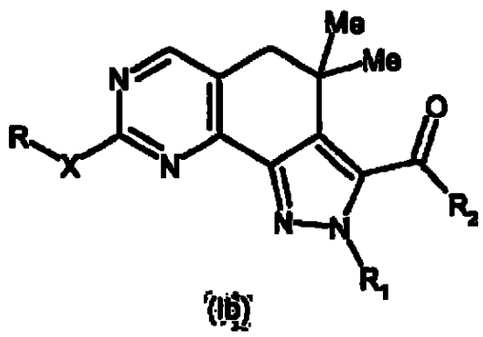


(XIIIb)

et. 12) hacer reaccionar un compuesto de fórmula (XIIIa) o (XIIb) con un derivado de guanidina de fórmula (VI), con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



(Ia)



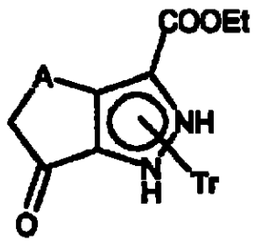
(Ib)

En donde R y R_1 son como se reportó anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

(4) cuando, en la fórmula (Ib), A es un grupo $-(CH_2)_2-$, grupo $-CH_2-C(CH_3)_2-$, grupo $-C(CH_3)_2-CH_2-$, R_1 esta directamente ligado

a R_2 con el fin de producir una estructura de anillo tetracíclica:

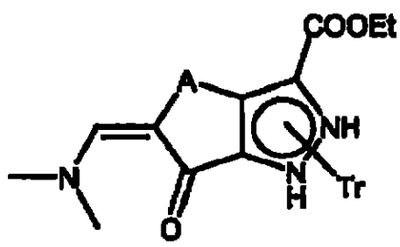
et.13) Hacer reaccionar un compuesto de fórmula,(IV), (IX), (XII) en donde R_1 es hidrógeno, obtenido de acuerdo a (et.2), (et.6), (et.10) del proceso, con cloruro de trifenilmetilo con el fin de obtener un compuesto de fórmula (XIV).



(XIV)

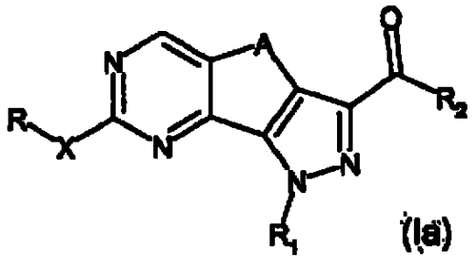
En donde Tr representa tritil(trifenilmetil);

Et.14) hacer reaccionar el compuesto de fórmula (XIV) con dimetilformamida-di-terc-butilacetato, como se estableció en la etapa (et.3), con el fin de obtener un compuesto de fórmula (XV)

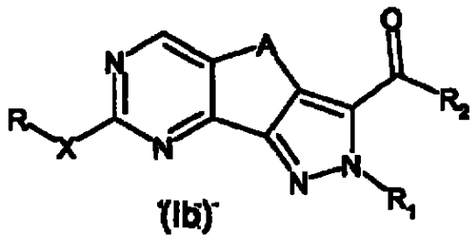


(XV)

et.15) hacer reaccionar el compuesto de fórmula (XV)con un derivado de guanidina adecuado de fórmula (VI), como se estableció en la etapa (et.4b), con el fin de obtener un compuesto de fórmula (Ia) o (Ib).



(Ia)



(Ib)

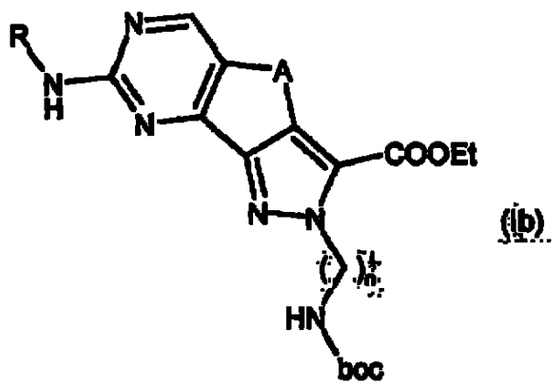
donde R es como se definió anteriormente, A es un grupo $-(CH_2)_2-$, grupo $-CH_2-C(CH_3)_2$, grupo $-C(CH_3)_2-CH_2-$, X es NH, R_1 es tritilo y R_2 es etoxi;

et.16) hacer reaccionar el compuesto anterior de la Fórmula (Ia) o (Ib) bajo condiciones acídicas, con el fin de obtener el compuesto correspondiente de fórmula (Ia)o (Ib) en donde R_1 es hidrógeno;

et.17) hacer reaccionar el compuesto anterior de fórmula (Ia) o (Ib) con un agente aquilatante adecuado de fórmula (XVI) en la presencia de terc-butilato de litio

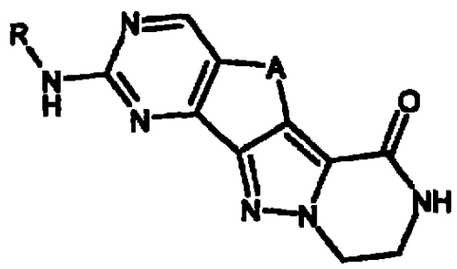
$$Br-(CH_2)_n-NH-BOC \qquad (XVI)$$

En donde n es 2 o 3, con el fin de obtener un compuesto de fórmula (Ib)

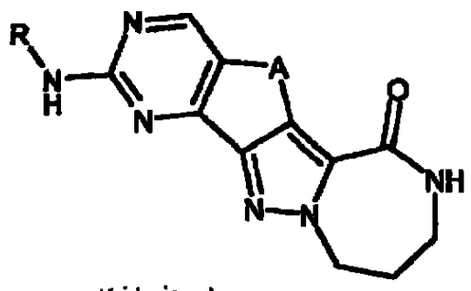


En donde A, n y R son como se definió anteriormente;

et.18) hacer reaccionar el compuesto anterior de fórmula (Ib) bajo condiciones ácidas, con el fin de convertir el grupo ter-butoxicarbonilamino y el amino (desprotección) y hacer reaccionarlo con carbonato de cesio ($CsCO_3$) con el fin de obtener uno o cualquiera de los dos compuestos de fórmula (Ib)



(Id; n =2)

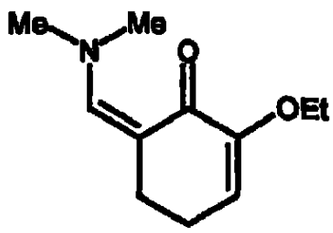


(Id; n =3)

En donde A y R es como se definió anteriormente, y opcionalmente convertirlos en otros derivados de fórmula (I);

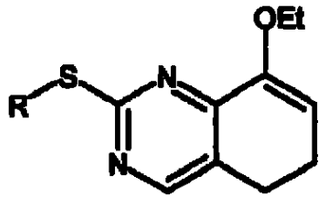
(5) cuando R_2 es un grupo voluminoso:

et.19) hacer reaccionar 2-etoxi-2-ciclohexenona con dimetilformamida-di-terc butilacetalo, como se reportó en la etapa (et.3), con el fin de obtener un compuesto de fórmula (XVII)



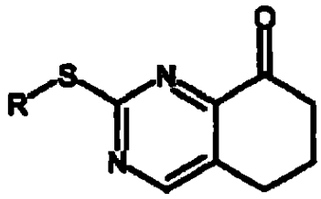
(XVII)

et.20) hacer reaccionar el compuesto de fórmula (XVII) con un derivado de fórmula (VII) de acuerdo a la etapa (et.4c), con el fin de obtener un compuesto de la fórmula (XVIII)



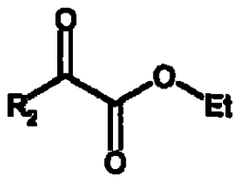
(XVIII)

En donde R es como se definió anteriormente; y subsecuentemente tratar este bajo de condiciones ácidas con el fin de obtener un compuesto de fórmula (XIX)



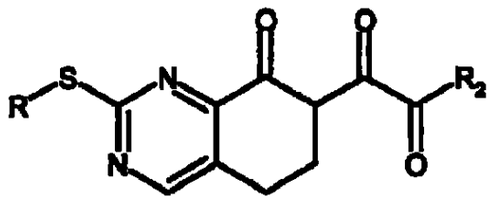
(XIX)

et.21) hacer reaccionar el compuesto de fórmula (XIX) con un compuesto de fórmula (XX)



(XX)

En donde R_2 es un grupo voluminoso con el fin de obtener un compuesto de fórmula (XXI)

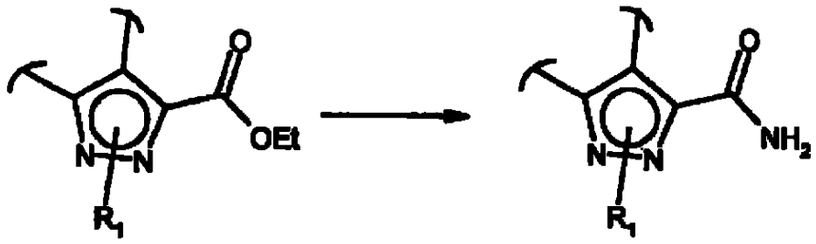


(XXI).

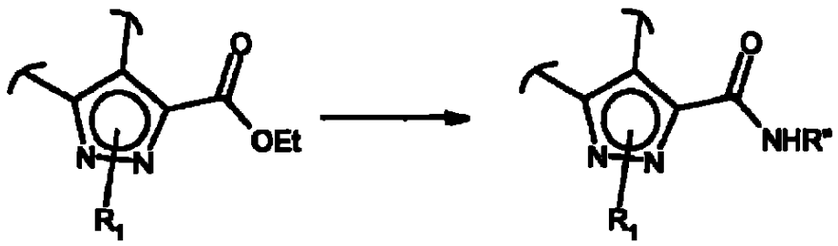
et.22) hacer reaccionar un compuesto de fórmula (XXI) con un derivado de hidrazina de fórmula (III), según la etapa (et.1) del proceso, con el fin de obtener un compuesto de fórmula (I) en donde R y R_1 son como sé definió anteriormente, X es -S- y R_2 es un grupo voluminoso; y opcionalmente convertirlos en otros derivados de fórmula (I)

Como se reportó anteriormente, los compuestos de fórmula (I) que son preparados de acuerdo con el proceso objeto de la invención como por ejemplo como se estableció en las etapas (et.4a), (et.4b), (et.4c), (et.8), (et.12), (et.13), (et.18), y(et.22), puede ser convenientemente convertidos en otros compuestos de fórmula (I) al operar de acuerdo con condiciones operativas bien conocidas. Como por ejemplo, los compuestos de fórmula (I).

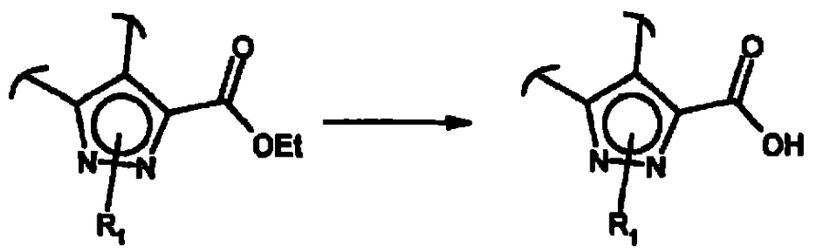
et.23) en donde R_2 es etoxi se puede convertir en los compuestos de fórmula (Ia) o (Ib) en donde R_2 es amino mediante el tratamiento con hidróxido de amonio



et.24) en donde R_2 es etoxi se puede convertir en los compuestos de fórmula (I) en donde R_2 es un grupo -NHR" mediante tratamiento con una amina de fórmula R"-NH_2 (XXII)



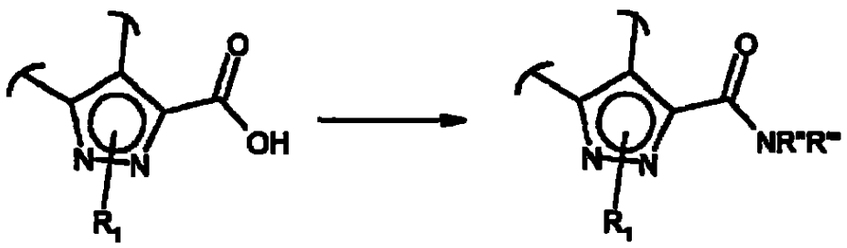
et.25) en donde R_2 es etoxi se puede convertir en los compuestos de fórmula (I) en donde R_2 es un grupo -OH a través de hidrólisis ácida o básica



et.26) en donde R_2 es -OH se puede convertir en los compuestos de Fórmula (I) en donde R_2 es un grupo -NR"R" o N(OH)R", a través de la reacción con un derivado de fórmula (XXIII) o (XXIV)

R"R'''NH (XXIII) R"NHOH (XXIV)

Bajo condiciones básicas y en la presencia de un agente de condensación adecuado



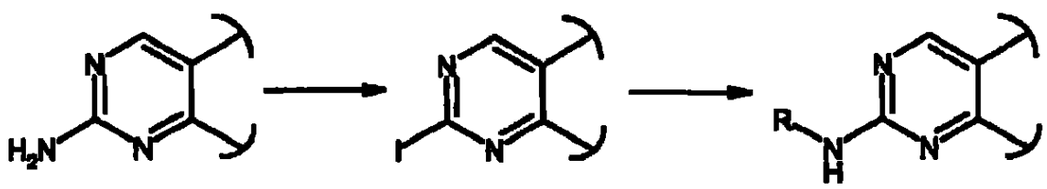
et.27) en donde R es hidrógeno y X es -NH- se puede convertir en los compuestos de fórmula (I) en donde R es diferente de hidrógeno, como se definió anteriormente, y X es -CONH-, a través de la reacción con un haluro ácido, por ejemplo cloruro, de fórmula R-COCl (XXV)



et.28) en donde R es hidrógeno y X es -NH- se puede convertir en los compuesto de fórmula (I) en donde R es diferente de hidrógeno, como se definió, y X es -NH-CO-NH-, a través de la reacción con un isocianato de fórmula R-NCO (XXVI)

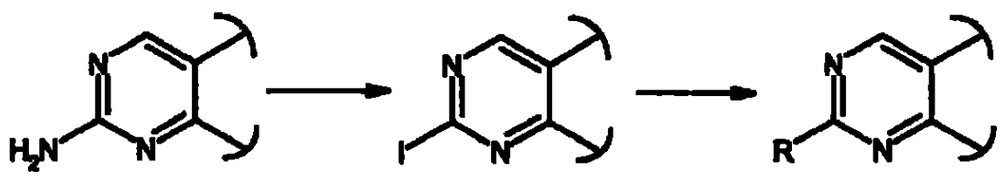


et.29) en donde R es hidrógeno y X es -NH- se puede convertir en los compuesto de fórmula (I) en donde R es arilo y X es -NH-, al convertir primero grupo amino a yodo con isoamilnitrito y diyodometano o yoduro de cesio, en la presencia de yoduro y CuI, y al reaccionar subsecuentemente con un derivado de yodo con arilamina de fórmula $R-NH_2$ (XXVII), en la presencia de acetato de paladio y (2,2´-bis(difenilfosfino))-1,1´-binaftaleno (BINAP)

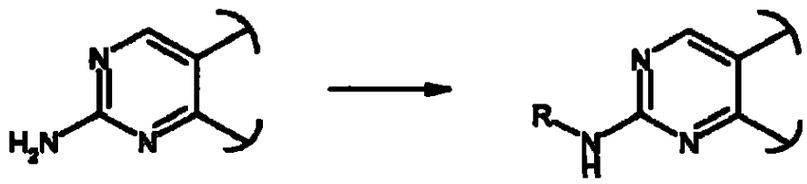


et.29a) en donde R es hidrógeno y X es -NH- se pueden convertir en los compuestos de fórmula (I) en donde R es alquilo, cicloalquilo, cicloalquil-alquilo ,arilalquilo, heterociclilo, herociclilalquilo, y X es -NH-, al convertir primero el grupo amino a yodo, como se describió en la etapa previa (et.29), y al hacer reaccionar subsecuentemente el derivado de yodo con alquilo, cicloalquilo, cicloalquilo-alquilo, heterociclilo o heterociclilamina de fórmula RNH_2 (XXVII), en donde R es como se definió allí;

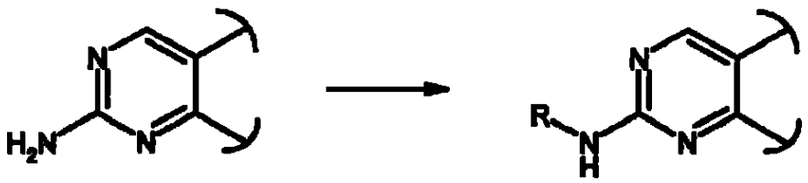
et.30) en donde R es hidrógeno y X es -NH- se pueden convertir en los compuestos de fórmula (I) en donde R es arilo y X es un enlace sencillo, al convertir primero el grupo amino a yodo, como en la etapa anterior (et.29), y al hacer reaccionar subsecuentemente el derivado de yodo con un ácido arilborónico de fórmula $R\text{-}B(OH)_2$ (XXVIII), en la presencia de un derivado de paladio



Et.31) En donde R es hidrógeno y X es -NH- se pueden convertir en los compuestos de fórmula (I) en donde R es alquilo o arilmetilo, mediante la reacción de un alquil-aldehido o aril-aldehido de fórmula R-CHO (XXIX) en la presencia cianoborohidruro de sodio ($NaBH_3CN$) y ácido acético

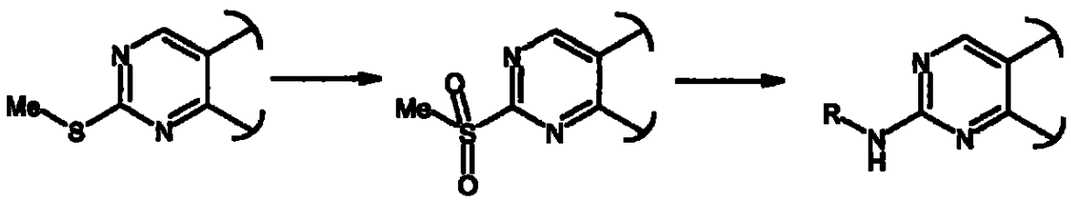


et.31a) en donde R es hidrógeno y X es -NH- se puede convertir en los compuestos de fórmula (I) en donde R es cicloalquilo o heterocicloalquilo, mediante la reacción con una cicloalquil cetona o heterocicloalquilcetona en la presencia de triacetoxiborohidruro de sodio ($NaBH(OAc)_3$) y ácido trifluoroacético

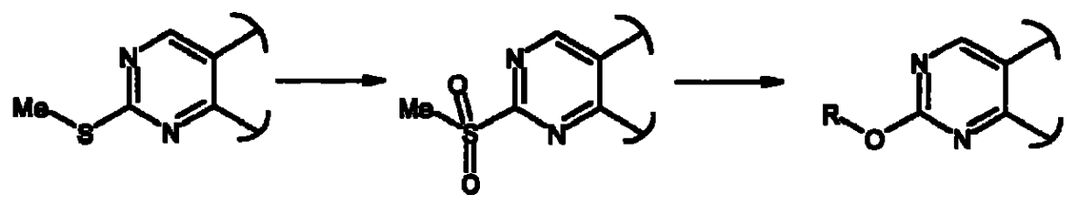


et.32) en donde R es como se definió anteriormente, por ejemplo, metilo, y X es -S- se puede convertir en los compuestos de fórmula (I) en donde R es un alquilo opcionalmente sustituido, cicloalquilo, heterociclilo,

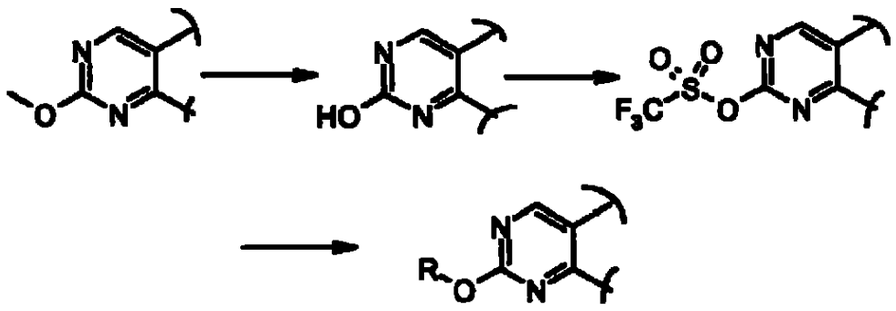
cicloalquil-alquilo, arilalquilo o heterociclilalquilo, al convertir primero el grupo RS- en RSO_2- bajo condiciones oxidativas, y luego al hacer reaccionar el derivado de sulfonilo con una amina de fórmula $R-NH_2$ (XXVII) en donde R es un alquilo opcionalmente sustituido, cicloalquilo, heterociclilo, cicloalquil-alquilo, arilalquilo o heterociclilalquilo



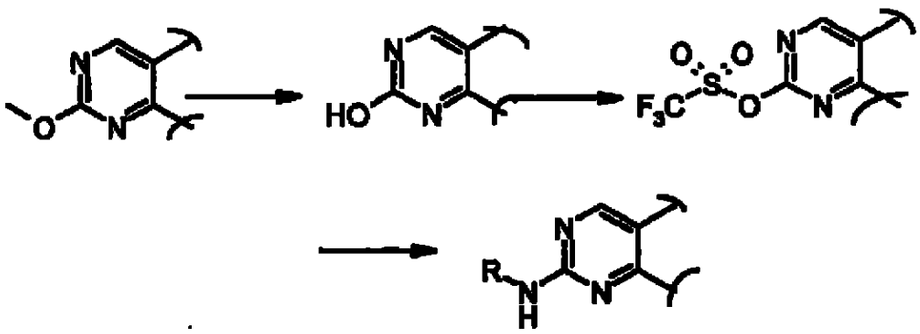
et.33) en donde R es como se definió anteriormente, por ejemplo, metilo, y X es -S- se pueden convertir en los compuestos de fórmula (I) en donde R es como se definió en la fórmula (I) y X es -O-, al convertir primero el grupo RS- en RSO_2- como en la etapa (et.32) y al luego hacer reaccionar el derivado de sulfonilo con un compuesto de fórmula R-OH (XXX)



et.33a) en donde R es metilo, y X es -O- se puede convertir en los compuestos de fórmula (I) en donde R es como se definió en la fórmula (I) y X es -O-, al convertir primero el grupo MeO- en HO-, luego hacerlo reaccionar con un agente triflatante con el fin de obtener el correspondiente trifluorometansulfonato y finalmente hacerlo reaccionar con un compuesto de fórmula R-OH (XXX)



et.33b) en donde R es metilo y X es -O- se puede convertir en los compuestos de fórmula (I) en donde R es un grupo alquilo, cicloalquilo, heterociclilo, cicloalquil-alquilo, heterociclilalquilo opcionalmente sustituido, y X es -NH-, al convertir primero el MeO- en HO-, entonces al hacerlo reaccionar con un agente triflatante con el fin de obtener el correspondiente trifluorometanosulfonato y finalmente al hacerlo reaccionar con la amina de fórmula $R-NH_2$ (XXVII) en donde R es un grupo alquilo, cicloalquilo, heterociclilo, cicloalquilalquilo, arilalquilo o heterociclilalquilo opcionalmente sustituidos



et.33c) en donde R es metilo y X es -O- se puede convertir en los compuestos de fórmula (I) en donde R es un arilo y X es-NH-, al convertir primero el grupo MeO- en -OH, luego hacerlo reaccionar con un agente triflatante con el fin de obtener trifluorometansulfonato correspondiente y finalmente hacerlo reaccionar con una amina de fórmula RNH_2 (XXVII) en donde R es un arilo opcionalmente sustituido en la presencia de acetato de paladio y BINAP;

et.34) en donde un es un grupo $-(CH_2)_2-$ se puede convertir en el compuesto de fórmula (I) en donde un es un grupo-CH=CH-, bajo condiciones operativas deshidrogenantes en la presencia de un catalizador Pd o Pt.

El proceso anterior, en cualquiera de las variantes anteriormente mencionadas, es un proceso análogo que se puede llevar un cabo de acuerdo con los métodos bien conocidos en la técnica.

De acuerdo con las etapas (et.1) del proceso, 2-etoxi-2-ciclohexen-1-ona se hace reaccionar con dietil oxalato en la presencia de $LiN(TMS)_2$ de un solvente adecuado tal como, por ejemplo, dioxano, tetrahidrofurano o dietil éter.

De acuerdo con la etapa (et.2a), el compuesto de fórmula (II) se hace reaccionar con un derivado de hidrazina adecuado de fórmula (III), en la presencia de un alcohol inferior tal como metanol, etanol o mezclas de estos. Preferiblemente, la reacción anterior es llevada acabo en etanol a temperatura de reflujo, con el fin de obtener una mezcla de ambos compuestos de fórmulas (IVa) y (IVb) en donde el anterior está presente en cantidades mayores. Su separación en los compuestos simples (IVa) y (IVb) es llevada a cabo bajo métodos convencionales, por ejemplo, a través de HPLC preparativo.

Al trabajar de acuerdo con la etapa (et.2b) del proceso, en su lugar, esto es al hacer reaccionar el compuesto de fórmula (II) con el derivado de hidrazina de fórmula (III) en la presencia de ácido acético, se obtiene un compuesto simple de fórmula (IVa). La reacción es preferiblemente llevada a cabo a temperatura ambiente de cuarto.

De acuerdo con la (et.2c) del proceso, el compuesto de fórmula (IVa) en donde R_1 es hidrógeno, reacciona con un compuesto de modo de fórmula (IVc) en la presencia de una base tal como hidruro de sodio en un solvente adecuado, por ejemplo tetrahidrofurano, dioxano o dimetilformamida, a una temperatura que varía desde temperatura ambiente de cuarto a 100° C, con el fin de obtener una mezcla de compuestos (IVa) y (IVb) en donde el anterior está presente en cantidades mayores, y al separarlos bajo métodos convencionales, por ejemplo a través HPLC preparativo.

De acuerdo con la (et.3) del proceso, el compuesto de fórmula (IVa) o (IVb) reacciona con dimetilformamida-di-terc-butilacetato, en la presencia de un solvente adecuado tal como, por ejemplo, dimetilformamida, con el fin de obtener los compuestos de fórmula (Va) o (Vb), respectivamente. Preferiblemente, las reacción es llevada a cabo a temperaturas que varian desde temperatura ambiente de cuarto hasta aproximadamente 70° C.

De acuerdo con una cualquiera de las etapas alternativas (et.4a), (et.4b), (et.4c) o (et.4d) del proceso, el compuesto de fórmula (Va) o (Vb) reacciona con guanidina, sales de guanidina o derivados de estos, alquilisotiourea o metilisourea con el fin de obtener el compuesto

correspondiente de fórmula (Ia) o (Ib) a través de la formación de anillo de pirimidina.

Cualquiera de las reacciones anteriores es llevada a cabo de acuerdo con métodos convencionales. Como un ejemplo, las reacciones con guanidina o sales de estas tal como clorhidrato, carbonato o nitrato, o con el derivado guanidina de fórmula (VI), como se estableció en las etapas (et.4a) o (et.4b), son llevadas a cabo en un solvente alcoholico inferior bajo condiciones neutras o básicas, preferiblemente con etanol y etilato de sodio o con diazabicicloundeceno (DBU) a temperatura de reflujo o, alternativamente, en dimetilformamida a una temperatura que varía desde 80° C a temperatura de reflujo en la presencia de carbonato de potasio. La reacción con alquilisotiourea (VII), en (et.4c), es llevada a cabo en la presencia de acetato de potasio y en un solvente adecuado tal como dimetilformamida a temperatura de reflujo.

La reacción con metilisourea (et.4d) es llevada acabo en un solvente adecuado tal como acetonitrilo y en la presencia de una base tal como carbonato de potasio a temperatura de reflujo.

Las reacciones de las etapas (et.5) y (et.6) son llevadas acabo bajo condiciones operativas establecidas en las etapas (et.1), (et.2a) o (et.2b) y conduce a los compuestos deseados de fórmula (IXa) o (IXb), respectivamente.

etapa (et.7) del proceso es preferiblemente llevada a cabo al hacer reaccionar el derivado de fórmula (IXa) o (IXb) con etil formato bajo condiciones básicas, preferiblemente en la presencia de etilato de sodio o hidruro de sodio de un solvente adecuado tal como, por ejemplo, dietil eter, tetrahidrofurano o dioxano, a una temperatura que varía desde temperatura ambiente a temperatura de reflujo.

Las condiciones de reacción de la etapa (et.8) son aquellas previamente reportadas para las etapas (et.4a y et.4b).

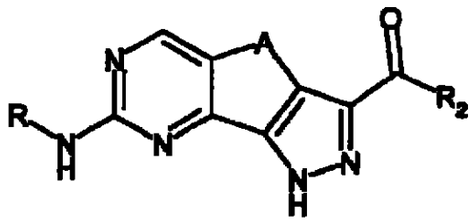
De acuerdo con la etapa (et. 9), 2-metoxi-5,5-dimetil-2-ciclohexen-1-ona reacciona con dietil oxalato en la presencia de hidruro de sodio en un solvente adecuado tal como dietil eter, tetrahidrofurano o dioxano, a temperatura de reflujo.

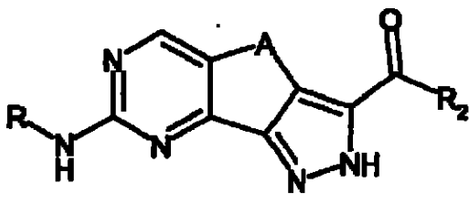
Las condiciones de reacción subsecuentes de las etapas (et.10) son esencialmente aquellas previamente reportadas par alas etapas (et.2a) o (et.2b), y aquellas etapas (et.11) y

(et.12) corresponden aquellos de (et.3) y (et.4a y et.4b), respectivamente.

De acuerdo con la etapa (et.13) del proceso, es claro para el experto que ambos compuestos de fórmula (IVa) y (IVb) en donde R1 es un átomo hidrógeno son forma tautoméricas de un compuesto dado que pueden ser convenientemente identificadas por tener la fórmula (IV). A este respecto, el mismo derivado reacciona con trifenilmetil cloruro con el fin de obtener un compuesto de fórmula (XIV) en donde uno cualquiera de los dos átomos de nitógeno pirazol son alquilatados con un grupo tritilo (por ejemplo trifenilmetilo).

Las condiciones operativas en la etapa (et.14) y (et.15) del proceso corresponde esencialmente aquellas reportadas ya par alas etapas de (et.3) y (et.4a y et.4b). De acuerdo con la etapa (et.16), el grupo tritilo de los compuestos de fórmula (I) es removido bajo condiciones ácidas, por ejemplo con ácido trifluoroacético y en la presencia de un solvente adecuado tal como diclorometano, con el fin de dar origen al compuesto correspondiente de fórmula (I) en donde R_1 es hidrógeno, en ambas formas:





Su alquilación subsecuente con un derivado de (XVI), de acuerdo a la etapa (et.17) del proceso, permite alquilatar selectivamente el átomo de nitrógeno pirazol que está en proximidad del grupo -COOEt; esta reacción se puede llevar acabo con terc-butilato de litio y en un solvente adecuado, tal como dioxano, dietil éter o tetrahidrofurano.

De acuerdo con la etapa (et.18), el compuesto anterior es convertido primero en el derivado amino libre al trabajar de acuerdo con métodos convencionales, por ejemplo bajo condiciones ácidas, preferiblemente con ácido clorhídrico, en un solvente adecuado tal como dioxano a temperatura de reflujo, y subsecuentemente ciclizado al derivado tetraciclíco deseado en la presencia de una base tal como carbonato de cesio ($CsCO_3$) y en un solvente adecuado tal como un alcohol inferior preferiblemente metanol, que varía de una temperatura ambiente a reflujo.

Las condiciones operativas de las etapas (et.19) y (et.20) del proceso corresponden esencialmente a aquellas ya reportadas para las etapas (et.3) y (et.4c); el tratamiento a

sido subsecuente del compuesto de fórmula (XVIII) al compuesto de fórmula (XIX) es preferiblemente llevado acabo con una solución acuosa de ácido acético a una temperatura aproximadamente de 100°C.

De acuerdo con la etapa (et.21), el compuesto de fórmula (XIX) reacciona con un derivado adecuado de fórmula (XX) en la presencia de hidruro de sodio y en un solvente adecuado, por ejemplo, dietileter, tetrahidrofurano o dioxano, a una temperatura que varía desde aproximadamente -50°C a temperatura ambiente.

Las condiciones operativas de la etapa (et.22) esencialmente corresponden a aquellas de la etapa (et.1) del proceso.

Como se indicó los compuestos de fórmula (I) preparados así pueden ser fácilmente convertidos en varios otros compuestos de fórmula (I) de la invención.

Como en ejemplo, los compuesto de fórmula (I) que llevan R_2 como un grupo de etoxi, o aun como un grupo de alcoxi, se pueden convertir en una variedad de derivados de acuerdo con métodos bien conocidos en la técnica para convetir grupos carboxiester ($-COOR_2$) en carboxamidas ($-CONH_2$), N-carboxamidas han sido sustituidas (-CONHR") y ácidos carboxílicos (-COOH), por ejemplo como se reportó en las etapas (et.23), (et.24) y (et.25).

Las condiciones operativas son aquellas ampliamente conocidas en la técnica que pueden comprender, por ejemplo en la conversión del grupo carboxiester en un grupo carboxamida, la reacción con amonio e hidróxido de amonio en la presencia de un solvente adecuado tal como un alcohol inferior dimetilformamida o mezclas de estos; preferiblemente la reacción es llevada acabo con hidróxido de amonio en una mezcla de metanol/dimetilformamida, a una temperatura que varía desde aproximadamente desde 50°C a aproximadamente 100°C.

Las condiciones operativas análogas aplican en la preparación de carboxamidas N- sustituidas en donde una amina primaria adecuada se utiliza en lugar de amonio o hidróxido de amonio.

De manera similar, los grupos carboxiéster se pueden convertir en derivados de ácido carboxílico a través de condiciones básicas o acidas, ampliamente conocidas en la técnica.

De acuerdo a la etapa (et.26)del proceso, los compuestos de fórmula (1) en donde R_2 es hidroxi (-COOH) se puede convertir en derivados de corboxamido (-CONR"R"') o [-CON (OH)R"] en donde R" y R"' son como se indicó anteriormente, también inclusive los compuestos en donde R" y R"' forman, como adjunto con el átomo de nitrógeno al cual ellos estén unidos, un grupo heteroarilo o heterociclilo de 5 a 6 miembros que

contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S.

La reacción es llevada acabo en la presencia de un amino de fórmula (XXIII) o de un compuesto de fórmula (XXIV), como puede ser el caso, a condiciones básicas, preferiblemente con N,N-diisopropil-N-etilamina o trietilamina, en un solvente adecuado tal como diclorometano, dimetilformamida, tetrahidrofurano, o dioxano, y en la presencia de un agente de condensación adecuado tal como N, N'-diciclohexilcarbodiimida (DCC), N- (3-dimetilaminopropil)-N'-etilcarbodiimida hidroclorido (EDCI) o O-(benzotriazol-1-il)-N, N, N', N'-tetrametilisouronio tetrafluoroborato (TBTU); las cantidades catalíticas de (benzotriazol-1-iloxi) tripirrolidinofosfonio hexafluorofosfato (PyBOP) también se pueden requerir.

Además, los compuestos de fórmula (I) en donde R-NH-es un grupo amino ($-NH_2$) puede ser fácilmente convertido en los correspondientes derivados carboxamido (-NHCOR) o ureido (-NHCONHR), como se estableció en las etapas (et.27) o (et.28) del proceso, respectivamente. Típicamente, la reacción con isocianato s desarrolla con hidruro de sodio en dimetilformamida aunque aquel con cloruro ácido puede ser llevado acabo en solvente adecuado tal como piridina,

tetrahidrofurano, etil acetato o dioxano, o una mezcla de ellos a una temperatura ambiente

Los compuesto de (I) en donde R-NH- representa un arilamino o un grupo heteroarilo amino, se pueden obtener mediante los correspondientes yodo derivados los cuales, a su ves, pueden ser preparados, mediante los compuestos de fórmula (I) en donde R-NH-es amino, como en la etapa (et.29) del proceso.

La preparación de los derivados de yodo se pueden llevar a cabo en un solvente adecuado tal como tetrahidrofurano, dietileter o dimetoxietano ,a una temperatura que varía desde temperatura ambiente a aproximadamente 70°C, y durante un tiempo de aproximadamente 8 horas a aproximadamente 48 horas.

La conversión subsecuente del yodo derivado, se puede llevar a cabo en un solvente adecuado tal como dimetilformamida, dimetoxietano o acetonitrilo y en la presencia de cantidades catalíticas de acetato de paladio, (2,2'-bis(difenilfosfino)-1,1'-binaftaleno (BINAP) y una base tal como carbonato de potasio, fosfato de potasio o carbonato de cesio, a un temperatura que varía desde temperatura ambiente a 110°C y durante un tiempo que varía desde aproximadamente 2 a aproximadamente 24 horas.

Se pueden obtener los compuestos de fórmula (I) en donde R es arilo y X es un enlace simple, como se reportó en la etapa

(et.30), del derivado de yodo anteriormente mencionado mediante la reacción con ácidos arilborónicos de fórmula (XXVIII) en un solvente adecuado tal como dimetilformamida, diclorometano, metanol, dimetoxietano o acetonitrilo, en la presencia de tris(dibenzilideneacetona) dipaladio (0) o tetrakis trifenilfosfino paladio [$Pd(PPh_3)_4$], opcionalmente en la presencia de fluoruro de cesio, a una temperatura que varía desde temperatura ambiente a 100°C.

Los compuestos de fórmula (I) en donde RNH- representa un alquilamino, cicloalquilamino, cicloalquil-alquilamino, heterociclilamino, heterociclilalquilamino se pueden obtener del correspondiente derivado de yodo como se estableció en la etapa (et.29a) del proceso. La reacción se puede llevar a cabo en un solvente adecuado tal como dimetilformamida, dioxano o acetonitrilo o sin solvente a una temperatura que varía desde 40°C a 120°C durante un tiempo que varía de 3 a 18 horas.

Los compuestos de fórmula (I) en donde R-NH-es amino pueden ser convertidos en los derivados de alquilamino o arilmetilamino de fórmula (I) como se reportó en (et.31), al operar en un solvente adecuado con una mezcla de solventes, por ejemplo, comprometiendo una mezcla 1: 1: 1 de ácido acético, metanol y agua.

Los compuestos de fórmula (1) en donde R-NH- es amino se pueden convertir en los correspondientes derivados cicloalquilamino o heterocicloalquilamino de fórmula (I) como se reportó en (et.31a), al operar en un solvente adecuado tal como cloruro de metileno, acetonitrilo, dimetilformamida.

Los compuestos de fórmula (I) en donde R-X- representa un grupo alquiltio (R-S-) se pueden se pueden convertir en una variedad de compuestos de fórmula (1) en donde X es-NH-, al oxidar primero el grupo alquiltio a alquilsulfonilo y al reemplazarlo con un grupo R-NH- como reporto en (et.32). La etapa oxidativa se puede llevar a cabo por ozono en la presencia de un solvente adecuado, solvente adecuado, preferiblemente dimetilformamida o dimetilsulfoxido a temperatura ambiente; el reemplazo subsecuente del grupo alquilsulfonilo con un derivado amino adecuado es llevado acabo preferiblemente en la presencia de dimetilsulfoxido, dimetilformamida, dimetoxietano, dioxano, acetonitrilo, N-metil-pirrolidona o diglima, a temperatura que varía desde temperatura ambiente a aproximadamente 100°C.

De manera interesante, cuando se lleva acabo la ultima etapa en la presencia de dimetilsulfóxido como un solvente adecuado as a solvente adecuado, este mismo solvente puede actuar como tangente oxidante capaz de desarrollar los compuestos deseados en donde A representa un grupo-CH=CH-. Estos últimos

derivados son entonces separados de la mezcla de reacción de acuerdo a métodos convencionales, mediante cromatografía HPLC preparativo.

De acuerdo con la etapa (et.33) del proceso, los compuestos de fórmula (1) en donde X es-O- puede ser fácilmente obtenidos al hacer reaccionar el derivado sulfonilo con un derivado de o fenol de fórmula (XXX) en donde R es como en la fórmula (I). La reacción se puede llevar a cabo en la presencia de una base tal como carbonato de potasio o sodio, butilito litio, litio amida, sodio hidruro o similar, en un solvente adecuado tal como dimetilformamida o tetrahidrofurano, y al trabajar a una temperatura que varía de temperatura ambiente a aproximadamente 100°C.

Alternativamente, de acuerdo con las etapas (et.4d) y (et.33a), los compuestos de fórmula (I) en donde X es-O- se pueden obtener al hacer reaccionar los compuestos de fórmula (Va) y (Vb) con sulfato de metilisourea al operar en un solvente adecuado tal como dioxano, dimetilformamida o acetonitrilo en la presencia de una base tal como carbonato de sodio o potasio a una temperatura que varía desde 50°C a 100°C. Los compuestos de fórmula (I) en donde X es-O-y R es un hidrógeno se pueden obtener al hacer reaccionar los compuestos de fórmula (1) en donde X es-O-y R es metilo con trimetilsililo cloruro en la presencia de yoduro de sodio y

en un solvente adecuado tal como dioxano, tetrahidrofurano o acetonitrilo a temperatura ambiente. Los compuestos de fórmula (I) en donde X es-O- y R es un grupo trifluorosulfonilo se pueden obtener al hacer reaccionar los compuestos de fórmula (1) en donde X es-O-y R es hidrógeno con un agente triflatante tal como anhídrido trifluorometanosulfónico, trifluorometanosulfonilcloruro o N-fenil-bis (trifluorometanosulfonimida), opcionalmente en la presencia de una base tal como trietilamina o N, N-diisopropil-N-etilamino (DIPEA), en un solvente adecuado tal como diclorometano, tetrahidrofurano o dioxano a una temperatura que varía desde -78°C a temperatura ambiente.

Los compuestos de fórmula (I) en donde X es-O-y R es como se describe anteriormente se pueden obtener la hacer reaccionar los compuestos de fórmula (I) en donde X es-O-y R es un grupo trifluorometanosulfonilo con un alcohol o fenol de fórmula (XXX) en donde R es como en la fórmula (I), al operar en un solvente adecuado tal como dioxano, tetrahidrofurano, dimetoxietano, acetonitrilo, dimetilformamida o dimetilsulfoxido, a una temperatura que varía desde temperatura ambiente a aproximadamente 90°C, opcionalmente en la presencia de una base tal como carbonato de potasio, tercbutóxido de potasio o hidruro de sodio.

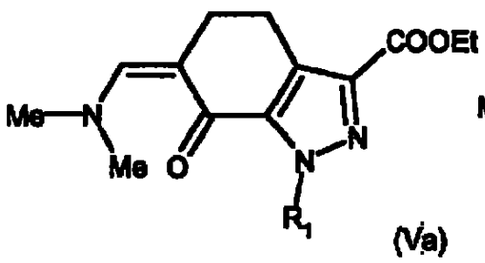
Alternativamente la reacción se puede llevar a cabo en un adecuado tal como tolueno, dimetilformamida, dimetoxietano o acetonitrilo, en la presencia de acetato de paladio, (±)-BINAP y una base tal como fosfato de potasio (K_3PO_4) o carbonato de potasio o cesio (K_2CO_3 o $CsCO_3$) una temperatura que varía desde 0°C a 100°C (et.33c).

Los compuestos de fórmula (I) en donde X es-NH-y R es un alquilo opcionalmente sustituido, cicloalquilo, heterociclilo, cicloalquil-alquilo o un grupo heterociclilalquilo se pueden obtener al hacer reaccionar los compuestos de fórmula (1) en donde X es-O-y R es un grupo trifluorometanolsulfonilo con una amina de fórmula $R-NH_2$ (XXVII) en donde R es como en la fórmula (I), al operar en un solvente adecuado tal como dioxano, tetrahidrofurano, dimetoxietano, acetonitrilo, dimetilformamida o dimetilsulfoxido, a una temperatura que varía de temperatura ambiente a 90°C, opcionalmente en la presencia de una base tal como carbonato de potasio o trietilamina.

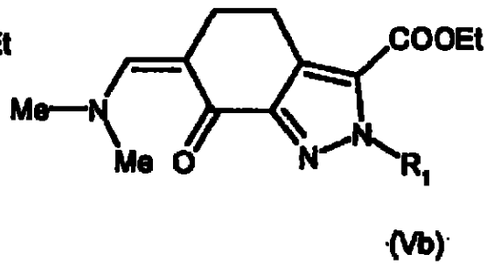
Finalmente, cualquiera de los compuestos de fórmula (1) en donde A representa un grupo $-CH_2-CH_2-$ puede sufrir deshidrogenación en la presencia de un catalizador de paladio o platino opcionalmente soportado, con el fin de dar origen a un derivado aromático donde A es -CH=CH-, como para (et.34) del proceso.

Ver la sección experimental para cualquier ejemplo específico concerniente a la preparación de los compuestos de fórmula (I) de la invención y su conversión a otros compuestos de fórmula (I).

Los compuestos intermedios de fórmula (Va) o (Vb) de acuerdo a la etapa (et.3)



(Va)



(Vb)

y en donde R_1 es un átomo de hidrógeno y un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 o ramificado, Cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo o heterociclilalquilo son novedosos y, de esta manera, representan un objeto adicional de la invención aparte de acuerdo a cualquier variante en el proceso para preparar los compuestos de fórmula (I), el material de partida y cualquier otro reactivo es conocido o fácilmente preparado de acuerdo a métodos conocidos

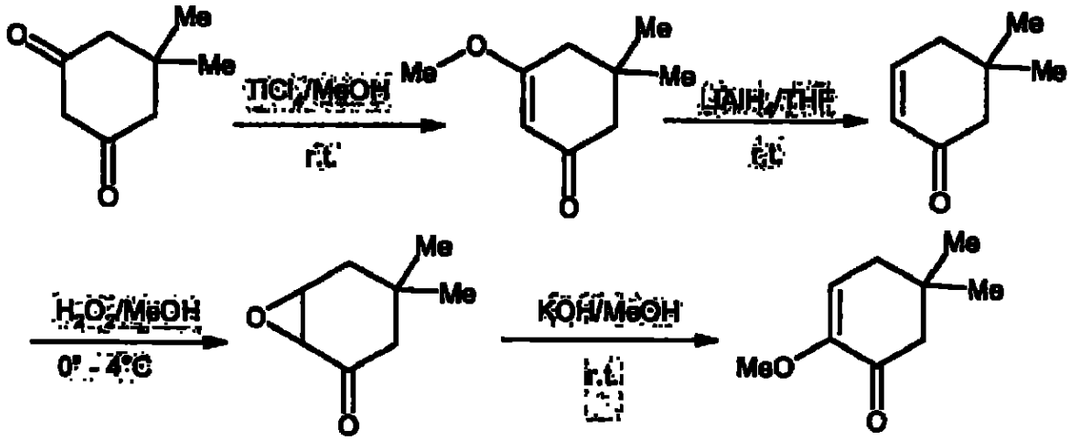
Como un ejemplo, 2-etoxi-2-ciclohexen-1-ona es un compuesto conocido que puede ser fácilmente obtenido a recluir

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ciclohexan-1, 2-diona con etanol en tolueno, en la presencia de cantidades catalíticas de ácido p-toluenesulfónico (TsOH).

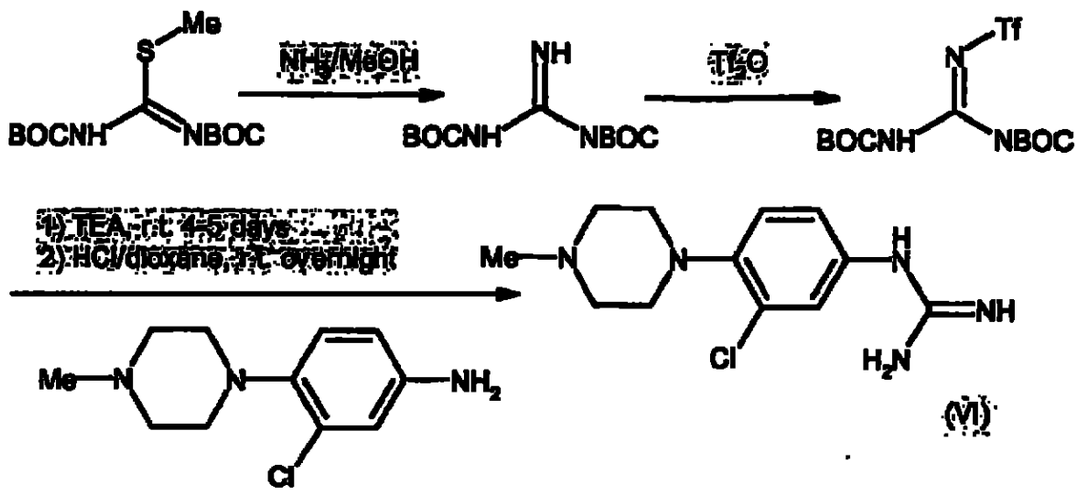
De manera similar, 2-metoxi-4, 4-dimetil-2-ciclohexen-1-ona es un compuesto conocido que se puede preparar a través de epoxidación de 4,4-dimetil-2- ciclohexen-1-ona comercialmente disponible y tratamientos subsecuente del epoxido con hidróxido de potasio en metanol.

Finalmente, 2-metoxi-5, 5-dimetil-2-ciclohexen-1-ona se puede preparar de acuerdo con el siguiente esquema de 5, 5-dimetil-ciclohexan-1, 3-diona comercialmente disponible:



Los compuestos de fórmula (III), (VI), (VII), (XVI), (XXII), (XXIII), (XXIV), (XV), (XXVI), (XXVII), (XXVIII), (XXIX) y (XXX) son conocidos o fácilmente preparados de acuerdo a métodos conocidos.

Justo como un ejemplo, cuando se preparan dando derivados guanidino de fórmula (VI) en donde R es una porción químicamente más compleja, puede ser seguido el siguiente esquema:



De todos los anteriores, es claro para el experto que cuando se preparan los compuestos de fórmula (I) de acuerdo a una cualquiera de las variantes del proceso anteriormente mencionados, los grupos funcionales opcionales dentro de los materiales de partida de los intermedios de estos y que pudieran dar origen a reacciones colaterales no deseadas, necesitan ser adecuadamente protegidos de acuerdo a técnicas convencionales. De manera similar, la conversión de estos últimos en compuestos desprotegidos libres pueden ser llevados a cabo de acuerdo a procedimientos conocidos.

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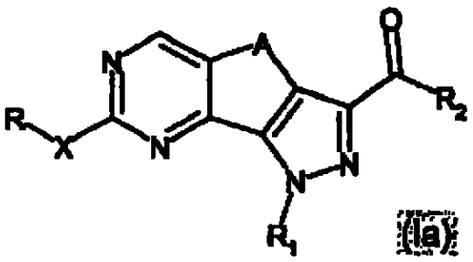
Como se apreciara fácilmente, si los compuestos de fórmula (I) preparados de acuerdo al proceso descrito anteriormente se obtienen como una mezcla de isómeros, su separación en isómeros simples de fórmula (I), de acuerdo a técnicas convencionales, esta dentro del alcance de la presente invención.

Las técnicas convencionales para resolución de erasomatos incluyen, por ejemplo, cristalización participada de derivados de sales de diastereoisomericas o HPLC quiral preparativo.

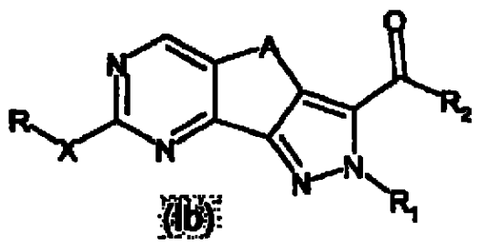
Además, los compuestos de fórmula (I) de la invención también se pueden preparar de acuerdo a técnicas químicas combinatorias ampliamente conocidas en el arte, por ejemplo al lograr las reaccione anteriormente mencionadas entre varios intermedios de una manera en serie y al trabajar bajo condiciones de síntesis de fase sólida (SPS).

Para una referencia en general a la preparación de los compuestos de fase (I) de la invención de acuerdo a técnicas de química combinatoria ver la sección experimental.

De esta manera, es un objeto adicional de la presente invención una librería de (Ia) o (Ib)



(Ia)



(Ib)

En donde

R es hidrógeno o un grupo opcionalmente sustituido seleccionado de amino, Alquilo C_1-C_6, cicloalquilo, C_3-C_{10} ciclo alquilo-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo;

X es un enlace simple o un radical divalente seleccionado de NR'-, -CONR'-, -NH-CO-NH-, -O-, -S-o-SO_2-, en donde R' es hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6, Cicloalquilo C_3-C_6, cicloalquilo-alquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos estén unidos, R y R' pueden formar un grupo de heteroarilo o heterociclilo de 5 o 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

R_1, unido a una cualquiera de los átomos de nitrógeno del anillo de pirazolo como para la fórmula (Ia) o (Ib), representa un átomo de hidrógeno o un grupo opcionalmente sustituido seleccionado de Alquilo C_1-C_6, Cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo o heterociclilalquilo o, en

la fórmula (Ib), R_1 es un grupo divalente (CH_2) n-NH-esta unido o enlazado R_2, en donde n es 2 o 3;

R_2 es un grupo seleccionado -NR"R"', -N(OH)R",-OR" o -R" en donde R" y R"' son cada uno independientemente, hidrógeno o un grupo opcionalmente sustituido seleccionado de Alquilo C_1-C_6, cicloalquilo C_3-C_6 o cicloalquilo-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo o, junto al átomo de nitrógeno al cual ellos están unidos, R" y R"'pueden formar un grupo de hetereoarilo o hetericilil0 de 5 o 6 miembros, qué contiene opcionalmente un heteroátomo seleccionado N, O o S;

A es un grupo divalente seleccionado de-CH_2-,-$(CH_2)_2$-,-CH_2-$C(CH_3)_2$-,-C $(CH_3)_2$-CH_2-o-CH=CH-;

o una farmacéutica mente aceptable de estos.

FARMACOLOGÍA

Los compuestos de fórmula (I) son activos como inhibidores de proteínas quinasa y son por lo tanto útiles, por ejemplo, para restringir la proliferación no regulada de células tumorales.

En terapia, ellos se pueden utilizar en el tratamiento de varios tumores, como a aquellos anteriormente reportados, así como también en el tratamiento de otros desordenes

proliferativo de células tal como psoriasis, proliferación de célula lisa vascular asociada con aterosclerosis y estenosis y restenosis post-quirúrgica y en el tratamiento de enfermedad de Alzheimer.

La actividad inhibitoria de los inhibidores seca es la cdk cíclica putativos y la potencia de los compuestos seleccionados se determina a través de un método de ensayo basado en el uso de la tecnología SPA (Amersham Pharmacia Biotech).

El ensayo consiste de la transferencia de una porción substrato radiactivamente marcada mediante la quinasa a un substrato biotinilado. El producto biotinilado resultante marcado con 33P-se le permite unirse a glóbulos SPA recubiertos con estreptavidina (capacidad deviotina 130 pmol/mg), y la dosis metida se midió mediante un contador de centelleó.

El ensayo de inhibición de actividad cdk2/Ciclina A

Reacción de quinasa: 4 µM de un substrato H1 de histona biotinilada en sitio (Sigma # H-5505), 10 1µM ATP (0.1 microCi $P^{33}\gamma$-ATP),1.1 nM de complejo Ciclina A/CDK2 inhibidor en un volumen final de un amortiguador 30 µl (TRIS HC1 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) fueron agregados a cada pozo 96 U de fondo. Después de incubación

durante 60 min. la temperatura ambiente, la reacción se detuvo por la adición de 100µl de amortiguador de PBS que contiene 32 mM EDTA, 500 µM de ATP frió, 0.1% Triton X100 y 10mg/ml de glóbulos de SPA recubiertos con streptavidina. Después de 20 minutos de incubación, 110 µL de suspensión fueron retirados y transferidos a un OPTIPLATE de 96 pozos que contiene 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 min con un lector de radioactividad de un conteo Packard TOP-.

Determinación IC_{50}: los inhibidores fueron ensayados a diferentes concentraciones que varían desde 0.0015 a 10 µM. Los datos experimentales fueron analizados por el programa de computadora GraphPad Prizm utilizando la ecuación logística de cuatro parámetros:

y = bottom+ (top-bottom)/(1+10^ ((logIC50-x) *slope))

Donde x es el logaritmo de la concentración inhibidora, y es la respuesta; y arranca en el fondo y va a la parte superior con una forma sigmoide.

Calculo Ki:

Método experimental: la reacción fue llevada a cabo en un amortiguador (10 mM Tris, pH 7.5, 10 mM MgCk, 0.2 mg/ml BSA, 7.5 mM DTT) que contiene 3.7 nM de enzima, histona y ATP

(proporción constante de ATP 1/3000 frío/marcado). Las reacciones fueron detenidas EDTA y el substrato capturado sobre fosfomembrana (platos de 96 Multipantalla de Millipore). Después de lavado extensivo, los platos multipantalla fueron leídos sobre un contador superior. Se midió el control (tiempo cero) para cada concentración de ATP histona.

Diseño experimental: las velocidades de reacción son medidas a cuatro ATP, substrato (histona) y concentraciones de inhibidos. La matriz de concentración en el pinto 80 se diseño alrededor del ATP respectivo y los valores inhibidor IC50 (0.3, 1,3, 9 veces el Km o los valores IC50). Un experimento concursote tiempo preliminar en ausencia del inhibidor y a diferente ATP y concentración de substrato permite la selección de un tiempo de punto final simple (10 min.) en el rango lineal de la reacción para la determinación del experimento Ki.

Estimados del parámetro cinético: los parámetros cinéticos fueron estimados mediante regresión cuadrada al menos no lineal simultanea utilizando [Es. 1] (inhibidor competitivo respecto a la ATP, mecanismo aleatorio) utilizando el conjunto de datos completo (80 puntos):

$$v=\frac{Vm\bullet A\bullet B}{\alpha\bullet Ka\bullet Kb+\alpha\bullet Ka\bullet B+\alpha\bullet Kb\bullet A+A\bullet B+\alpha\bullet\frac{Ka}{Ki}\bullet I\bullet(Kb+\frac{B}{\beta})}$$

Donde A= [ATP], B= [Substrato], I= [inhibidor], Vm= velocidad máxima, Ka, Kb, Ki las constantes de disociación del ATP, substrato inhibidor efectivamente, α y ß el factor de cooperatividad entre el substrato y el ATP que según el substrato y el inhibidor que se une respectivamente.

Además los compuestos seleccionados están caracterizados sobre un panel de quinasas sr/thre estrictamente relacionadas con el ciclo celular (cdk2/ciclina E, cdk1/ciclina B1, cdk5/p25, cdk4/ciclina D1), y también para especificar MAPK, PKA, EGFR, IGF1-R, Aurora-2 y Cdc 7.

Ensayo de inhibición de actividad cdk2/Ciclina E

Reacción de quinasa: 10 µM de un substrato de biotinilada en sitio (Sigma # H-5505), 30 µM ATP (0.3 microCi P33y-ATP), 4 mg GST-Ciclina E/CDK2 inhibidor en un volumen final de 30 µl de amortiguador (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) se agregaron a cada pozo de 96 U. Después de la incubación durante 60 min. a temperatura ambiente, la reacción se detuvo mediante la adición de 100 µl de

amortiguador PBS que contiene 32 mM de EDTA, 500 mM ATp frió, 0.1% de Triton X100 y 10mg/ml de estreptavidina de glóbulos de SPA a recubierto con estreptavidina. Después de 20 min. de incubación, 110 µL de suspensión fueron retirados y transferidos a OPTIPLATES de 96-pozos que contienen 100 µl de CsCl 5M. Después de 4 horas los pozos fueron leídos durante 2 minutos en un lector de radioactividad de conteo Packard TOP.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de actividad cdk1/ciclina B1.

Reacción de quinasa: 4 µM de un substrato H1 de histona biotinilada en sitio (Sigma # H-5505), 20 µM ATP (0.2 microCi P^{33} γ-ATP), 3 ng de complejo de ciclina B/CDK1, inhibidor en un volumen final de 30 µl de amortiguador (TRIS HCI 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) se agregaron a cada pozo de un fondo de 96 U. Después de 20 minutos a incubación a temperatura ambiente, la reacción se detuvo mediante 100 µl PBS + 32 mM EDTA + 0.1% Triton X-100 + 500 µM ATP, que contenía un 1 mg de glóbulos SPA. Luego un volumen de 110 µl es transferido al Optiplate.

Después de 20 min de incubación para captura de substrato, 100 µl CsCl 5M se agregaron para permitir la estatificación

de glóbulos a la parte superior del Optiplate permitir su asentamiento durante 4 horas antes del conteo de radioactividad en el instrumento Top-Count.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad cdk5/p25

Ensayo de inhibición de la actividad cdk5/p25 se desarrolló de acuerdo con el siguiente protocolo.

Reacción de quinasa: 10 µM de substrato H1 histona biotinilada (Sigma # H-5505), 30 µM ATP (0.3 microCi P^{33} γ-ATP), 15 ng de complejo CDK5/p25, inhibidor en un volumen final de amortiguador 30 µt (TRIS HCI 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) agregaron a cada pozo de un fondo de 96 U. Después de incubación durante 35 min a una temperatura ambiente, la reacción se detuvo mediante la adición de un amortiguador de 100 µl PBS que contiene 32 mM EDTA, 500 µM de ATP frío, 0.1% de Triton X100 y 10mg/ml de glóbulos SPA re cubiertos de estreptavidina. Después de 20 min incubación, 110 µL de suspensión se retiraron y se transfirieron a un OPTIPLATEs de 96-pozos que contienen 100 µl de CsCl 5M. Después de 4 horas los platos fueron leídos

durante 2 min en un lector de radioactividad TOP-Count Packard.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad cdk4/ciclina D1

Reacción de quinasa: 0,4 µM de substrato GST-Rb de ratón (769-921) (# sc-4112 de Santa Cruz), 10 µM ATP (0. 5 µCi P^{33} γ-ATP), 100 ng de GST- cdk4/GST-Ciclina D1 expresado de baculovirus, concentraciones adecuadas de inhibidor en un volumen final de amortiguador 50 µl (TRIS HC110 mM pH 7.5, $MgCl_2$ 10 mM, 7.5 mM DTT+ 0.2mg/ml BSA) se agregaron a cada pozo de un plato de 96 pozos con fondo con U. Después de 40 min a 37 °C de incubación, la reacción se detuvo mediante 20 µl EDTA 120 mM.

Captura: 60 µl fueron transferidos de cada pozo a un plato MultiScreen, para permitirle al substrato unirse al filtro de fosfocelulosa. Los platos entonces fueron lavados 3 veces con 150 µl/pozo PBS Ca+F/MgX libre y filtrado mediante un sistema de filtración MultiScreen.

Detección: Los filtros les permitió secar a 37°C, luego se agrego 100 µl/poso senteliante y un fragmento Rb marcado ^{33}P

se detecto mediante conteo de radioactividad el instrumento Top-Count.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad MAPK

Reacción de quinasa: 10 µM de un substrato MBP bitionilado en sitio (Sigma # M-1891), 15 µM ATP (0.15 microCi $P^{33}\gamma$-ATP), 30 ng GST-MAPK (Upstate Biotecnología # 14- 173), inhibidor en un volumen final de 30 µl de amortiguador (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) se agregaron a cada pozo de 96 con fondo en U. Después de la incubación de 35 min a temperatura ambiente, la reacción se detuvo mediante la adición de 100 µl de amortiguador PBS que contiene 32 mM EDTA, 500 µM de ATP frió, 0.1% de Triton X100 y 10mg/ml de estreptavidina de glóbulos SPA descubiertos con estreptavidina. Después de 20 min en incubación, 110 µL de suspensión fueron retirados y transferidos OPTIPLATES de 96-pozos que contienen 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 min en un lector de radioactividad TOP-Count Packard.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad PKA

Reaccion de Quinasa: 10 µ M de substrato histona H1 biotinilada en sitio(Sigma # H-5505), 10 µM ATP (0.2 microM $P^{33}\gamma$-ATP), 0.45 U PKA (Sigma # 2645), inhibidor en un volumen final de 30 µl de amortiguador (TRIS HCl 10 mM pH 7.5, $MgCl_2$ 10 mM, DTT 7.5 mM + 0.2 mg/ml BSA) se agregaron a cada pozo de 96 de fondo en U. Después de incubación durante 90 min a temperatura ambiente, la reacción se detuvo mediante la adición de 100 µl de amortiguador PBS que contenía 32 mM EDTA, 500 µM ATP frío, 0.1% de Triton X 100 y 10mg/ml de glóbulos SPA recubiertos con estreptavidina. Después de 20 min de incubación, 110 µL de suspensión fueron retirados y transferidos a un OPTIPLATES de 96 pozos que contenía 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 min en un lector de radioactividad Packard TOP-Count.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad EGFR

Reacción de Quinasa: 10 µM de substrato de MBP biotinilato en sitio (Sigma # M-1891), 2, µM ATP (0.04 microCi $P^{33}\gamma$-ATP), 36 ng de inhibidor GST-EGFR expresado en célula de insecto en un volumen final 30 µl de amortiguador (Hepes 50 mM pH 7.5,

$MgCl_2$ 3 mM, $MnCl_2$ 3 mM, DTT 1 mM, $NaVO_3$ 3 µM, + 0.2 mg/ml BSA) se agregaron a cada pozo de 96 de fondo en U. Después de la incubación de 20 min a una temperatura ambiente, la reacción se detuvo mediante la adición de 100 µl de amortiguador PBS y contenía 32 mM EDTA, 500 µM ATP frió, 0.1% de Triton X100 y 10mg/ml de glóbulos SPA recubiertos con estreptavidia. Después de 20 min de incubación, 110 µl de suspensión fueron retirados y transferidos a OPTIPLATEs de 96 pozos que contiene 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 min en un lector de radioactividad Packard TOP-Count

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad IGF1-R

El ensayo de inhibición de actividad IGF1-R se desarrolló de acuerdo con el siguiente protocolo.

Activación de Enzima: IGF1-R se debe activar mediante auto-fosforilación antes de arrancar con el experimento. Justo antes del ensayo, una solución de enzima concentrada (694 nM) se incuba por medio ahora de 28°C en presencia de 100 µM ATP y luego es llevado a una dilución de trabajo en amortiguador indicado.

Reacción de quinasa: 10 µM de substrato de péptido IRS1 biotinilado (PRIMM, 0-20 µM inhibidor, 6 µM ATP, 1 microCi ^{33}P-ATP, y 6 µM GST-IGF1-R (pre-incubador de 30 min a temperatura ambiente con 60 µM ATP frió) en un volumen final 30 µl de amortiguador (50 mM HEPES pH 7.9, 3 mM $MnCl_2$, 1 mM DTT, 3, µM $NaVO_3$) se agregaron a cada uno un plato de 96 pozos con fondo en U después de la incubación durante 35 min a temperatura ambiente, la reacción se detuvo mediante la adición 100 µl de amortiguador PBS que contiene 32 mM EDTA, 500 µM ATP frió, 0.1% de Triton X100 y 10 mg/ml de glóbulos SPA recubiertos con estreptavidina. Después de 20 min de incubación, 110 µL de suspensión se retiraron y transfirieron a un OPTIPLATES de 96 pozos que contienen 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 min en un lector de radioactividad de Packard TOP-Count.

Ensayo de inhibición de la actividad de Aurora-2

Reacció de quinasa: 8 µM péptido biotinilado (4 repeticiones de LRRWSLG), 10 µM ATP (0.5 uCi $P^{33}\gamma$-ATP), 7.5 ng Aurora 2, inhibidor en un volumen final de 30 µl de amortiguador (HEPES 50 mM pH 7.0, $MgCl_2$ 10 mM, 1 mM DTT, 0.2 mg/ml BSA, 3, µM ortovanadato) se agregaron a cada pozo de un plato de 96 con fondo en U. Después de 60 minutes de incubación a temperatura

ambiente, como la reacción se detuvo y el péptido biotinilado se capturo al agregar 100 µl de suspensión de glóbulos.

Estratificación: 100 µl de CsC12 5 M se agregaron a cada pozo y se les permitió asentarse 4 horas antes de que la radioactividad se contara en el instrumento Top-Count.

Determinación IC_{50}: Ver anterior

Ensayo de inhibición de la actividad Cdc7/dbf4

El ensayo de incubación de la actividad Cdc7/dbf4 se desarrolló de acuerdo con el siguiente protocolo.

El substrato de Biotin-MCM2 es trans-fosforilado mediante el conteo Cdc7/Dbf4 en la presencia de ATP con trazas de γ^{33}-ATP. El substrato de Biotin MCM2 fosforilado es luego capturado mediante glóbulos SPA recubiertos con Estreptavidina y la extensión de la fosforilación evaluada mediante conteo ß.

El ensayo de inhibición de actividad Cdc7/dbf4 se desarrolló en un plato de 96 pozos de acuerdo con el siguiente protocolo.

Cada pozo del plato se le agregó:

-10 µl substrato MCM2 (biotinilado,6 µM concentración final)

-10 µl enzima (Cdc7/Dbf4,17. 9 µM concentración final)

-10 µt de compuesto de ensayo (12 concentraciones crecientes en un rango de nM a µM para generar una curva de respuesta de dosis)

- 10 µl de una mezcla de ATP frío (2 µM concentración final) y ATP radioactivo (proporción 1/5000 molar con ATP frió) fue entonces utilizado arrancar la reacción que se le permitió tener lugar a 37°C.

El substrato, encima y ATP fueron diluidos en 50 mM HEPES pH 7.9 contiene 15 mM $MgCl_2$, 2 mM DTT, 3 µM $NaVO_3$, 2mM glicerofosfato y 0.2mg/ml BSA. El solvente para los compuestos de ensayo también contenía DMSO 10%.

Después la incubación de 60 minutos, la reacción se detuvo al agregar a cada pozo 100 µl de PBS pH 7.4 que contenía 50 mM EDTA, 1 mM ATP frió, 0.1% de Triton X100 y 10 mg/ml de glóbulos SPA recubiertos con estreptavidina.

Después de 20 min de incubación, con 110 µL de suspensión fueron retirados y transferidos a OPTIPLATES 96 de pozos que contienen 100 µl de CsCl 5M. Después de 4 horas, los platos fueron leídos durante 2 minutos en un lector de radioactividad Packard TOP-Count.

Determinación IC_{50}: Ver anterior

Los compuestos de la presente invención se pueden administrar bien sea como agentes simples o como alternativamente, de combinación con tratamientos anticáncer conocidos tal como régimen de terapia o quimioterapia de radiación en combinación con agentes citosestáticos o citotóxicos como, agente tipo antibiótico, agentes alquilatantes, agentes antimetabolito, agentes hormonales, agentes inmunológicos, agentes tipo interferon, inhibidores de ciclo oxiginasas, (ejemplo. g. COX-2 inhibidores), inhibidores de matrixmetaloproteasa, inhibidores de teloterasa, inhibidores de tirosina quinasa, agentes receptores del factor anticrecimiento, agentes anti-HER, agentes anti-EGFR, agentes anti-angiogénesis agentes (por ejemplo, inhibidores angiogénesis), inhibidores farnesil transferasa, inhibidores del camino de traducción de la señal ras-raf, inhibidores del ciclo de célula, inhibidores de otros inhibidores cdks, agentes de unión de tubulina, inhibidores de topoisomerasa I, inhibidores de topoisomerasa II, y similares.

Si se formula como una dosis fija, tales productos de combinación emplear los compuestos de esta dimensión dentro del rango de dosis descrito adelante y otro agente farmacéuticamente activo dentro del rango de dosis aprobado.

Los compuestos de fórmula (I) se pueden utilizar secuencial mente con agentes anticáncer conocidos cuando es inapropiada una formulación de combinación

Los compuestos de la fórmula (I) de la presente invención, adecuados para la administración a un mamífero, por ejemplo, a humanos, se pueden administrar en las rutas usuales y en el nivel de dosis que dependen de la edad, peso, condición del paciente y ruta de administración.

Por ejemplo, una dosis adecuada adoptada para la administración oral de un compuesto de formula (I) puede variar desde aproximadamente 10 a aproximadamente 500 mg por dosis, desde 1 a 5 veces diariamente. Los compuestos de invención pueden ser administrados en una variedad de formas de dosis, por ejemplo, oralmente, en la forma de tabletas, cápsulas, azúcar o tabletas recubiertas con película, las soluciones o suspensiones de líquido; rectalmente en la forma de supositorios; parenteralmente, por ejemplo, intramuscularmente, o a través de inyección o de infusión intravenosa y/o intratecal y/o intraespinal.

La presente invención también incluye composiciones farmacéuticas que comprenden un compuesto de fórmula (I) o una sal farmacéuticamente aceptable de estos en asocio con un

excipiente farmacéuticamente aceptable, que puede ser un portador o un diluyente.

Las composiciones farmacéuticas que contienen los compuestos de la invención son usualmente preparadas siguiendo métodos convencionales y son administradas en una forma farmacéutica adecuada.

Por ejemplo, las formas orales sólidas pueden contener, junto con el compuesto activo, diluyentes, por ejemplo, lactosa, dextrosa, sacarosa, sucrosa, celulosa, almidón de maíz o almidón de papa; lubricantes, por ejemplo, sílice, talco, ácido esteárico, estearato de magnesio o calcio, y/o polietilen glicoles; agentes de unión, por ejemplo, almidones, goma arábica, metilcelulosa de gelatina, carboximetilcelulosa o polivinil pirrolidona; agentes desintegrantes, por ejemplo, almidón, ácido algínico, alginatos o glicolato de almidón de sodio; mezclas efervescentes; sustancias de tinte, endulzantes, agentes humectantes tales como lecitina, polisorbatos, laurilsulfatos; y, en general, sustancias no tóxicas y farmacológicamente inactivas utilizadas en formulaciones farmacéuticas. Estas preparaciones farmacéuticas se pueden elaborar de manera conocida, por ejemplo, por medio de

mezclar, granular, formar tabletas, recubrir con azúcar, o procesos de recubrimiento de película.

Las dispersiones líquidas para administración oral pueden ser, por ejemplo, melazas, emulsiones y suspensiones.

Como un ejemplo, las melazas pueden contener, como portador, sacarosa o sacarosa con glicerina y/o manitol y sorbitol.

Las suspensiones y las emulsiones pueden contener, como ejemplos de portadores, goma natural, agar, alginato de sodio, pectina, metilcelulosa, carboximetilcelulosa, o polivinil alcohol.

Las suspensiones o soluciones para inyecciones intramusculares pueden contener, junto con el compuesto activo, el portador farmacéuticamente aceptable, por ejemplo, agua estéril, aceite de oliva, etil oleato, glicoles, por ejemplo, propilen glicol y, si se desea, una cantidad adecuada de clorhidrato de lidocaína.

Las soluciones para inyecciones intravenosas o infusiones pueden contener, como portador, agua estéril o preferiblemente pueden estar en la forma de soluciones

salinas estériles, acuosas, isotónicas, o ellas pueden contener propilen glicol como un portador.

Los supositorios pueden contener, junto con el compuesto activo, un portador farmacéuticamente aceptable, por ejemplo, manteca de cacao, polietilen glicol, una lecitina o tensoactivo de éster de ácido graso de polioxietileno sorbitan.

Con el objetivo de ilustrar mejor la presente invención, sin poseer ninguna limitación a ésta, son dados los siguientes ejemplos.

EJEMPLOS

Varios compuestos de fórmula (I), que incluyen de esta manera aquellos de fórmula (Ia) y (Ib) de la invención, se han preparado. Aunque algunos de ellos han sido específicamente nombrados y listados en la siguiente sección experimental, la mayoría han sido convenientemente identificados según un sistema de codificación de tablas reportados en la sección experimental, junto con sus datos analíticos.

Cada código, el cual identifica sin ambigüedad un compuesto específico simple de fórmula (I) solamente, consiste de cinco unidades B-X-M(C)-D.

El código B representa cualquier sustituyente R, según la fórmula (I), estando unido al resto de la molécula a través del enlace X; cada grupo B está representado a través de la fórmula química adecuada en la siguiente Tabla I, que indica también su punto de unión al resto de la molécula X-M.

El código X representa justo el grupo X de fórmula (I); sus significados están representados en la siguiente tabla II, que también indica su punto de unión al resto de la molécula M.

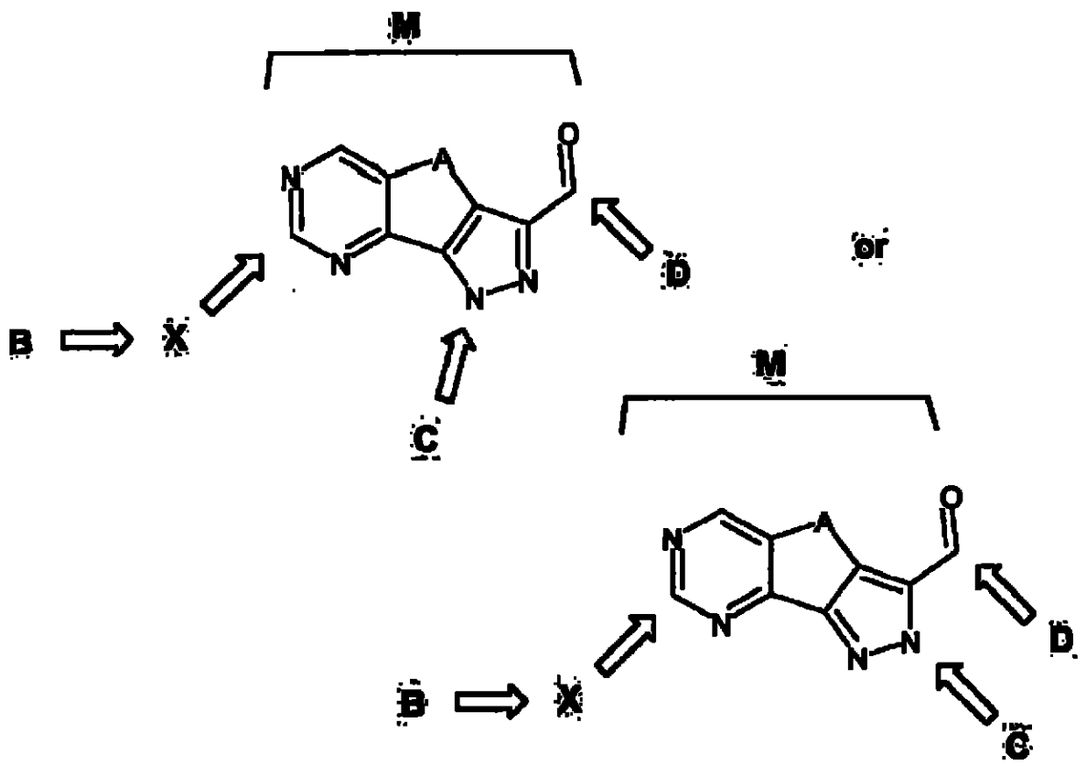
El código C representa el grupo R_1 que está unido al resto de la molécula a través de cualquiera uno de los átomos de nitrógeno del pirazol, según la fórmula (I). Cada grupo C está representado a través de una fórmula química adecuada en la siguiente tabla III, que indica también su punto de unión al resto de la molécula M.

El código D representa el grupo R_2 que está unido al resto de la molécula a través del grupo carbonilo, según la fórmula (I). Cada grupo D está representado a través de la fórmula

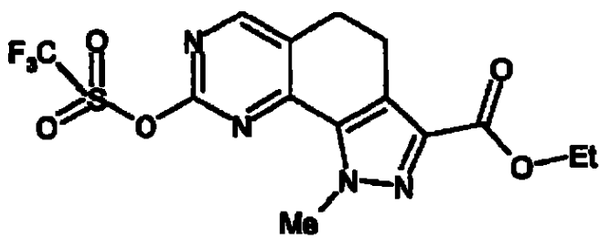
química adecuada en la siguiente tabla IV, que indica también su punto de unión al resto de la molécula M.

Finalmente, el código M se refiere al núcleo central de la molécula (I) que lleva un grupo carbonilo en la posición 3. De todo lo anterior es claro para la persona experta que M es sustituido por los grupos -X- (código X), R_1 (código C) y R_2 (código D), como se reportó en la fórmula (I); cada grupo M es representado a través de una fórmula química adecuada, en la tabla V, que también indica las posiciones de los otros sustituyentes.

Por lo tanto, el sistema de codificación actualmente utilizado para algunos compuestos de fórmula (I) se puede resumir de manera corta como sigue:



Justo como un ejemplo, que no pretende limitar el alcance de la presente invención, el compuesto B66-X03-M00(C01)-D01 (ver ejemplo 36) representa el derivado de pirazolo-quinazolina de fórmula (Ia) en donde el núcleo central está representado por la porción M00 de la tabla V, R es el grupo de fórmula B66 de la tabla I, X es el grupo divalente X03 de la tabla II, R_1 es el grupo C01 de la tabla III y R_2 es el grupo D01 de la tabla IV, que tiene la fórmula

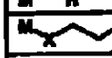


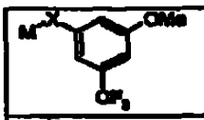
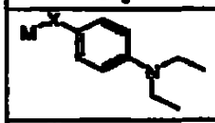
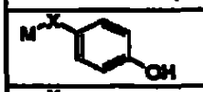
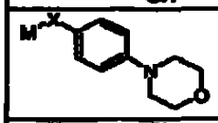
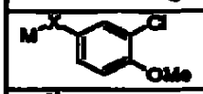
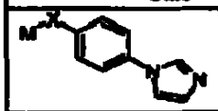
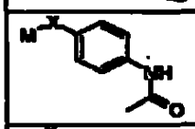
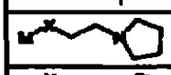
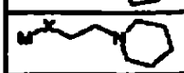
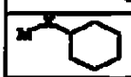
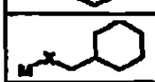
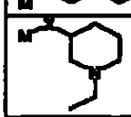
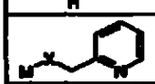
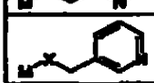
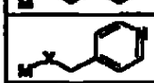
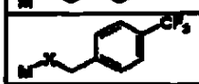
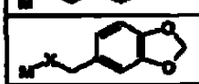
B68-X03-M00(C01)-D01

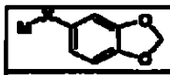
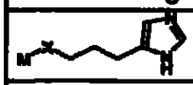
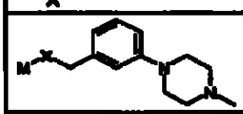
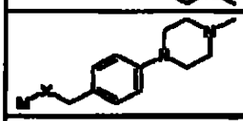
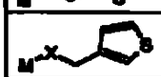
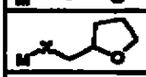
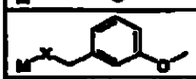
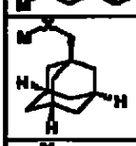
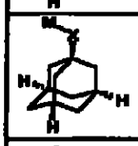
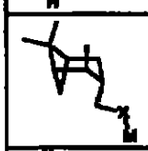
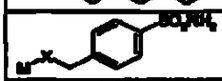
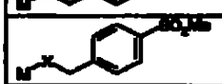
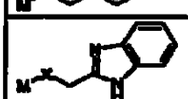
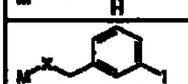
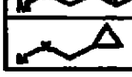
De todo lo anterior, es claro para la persona experta que cuando R_1 y R_2 están ligados juntos según la fórmula (Ib), entonces este ciclo adicional ya está incluido en la estructura de la porción M y, de esta manera, los códigos C y D se pierden.

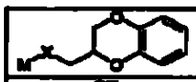
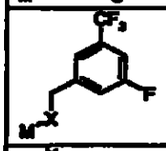
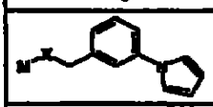
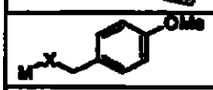
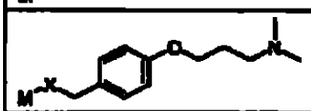
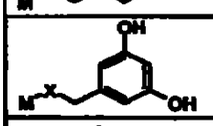
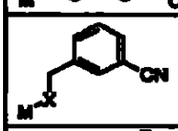
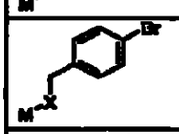
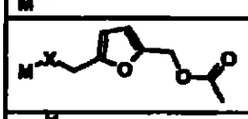
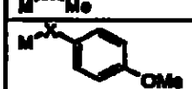
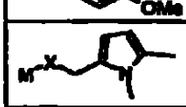
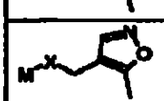
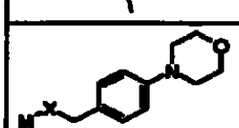
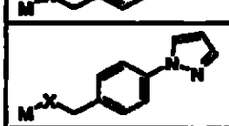
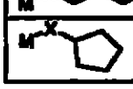
Tabla I

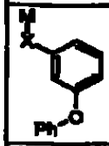
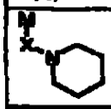
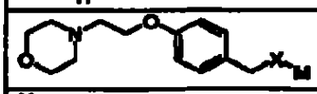
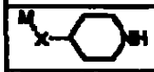
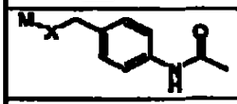
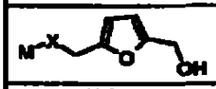
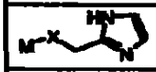
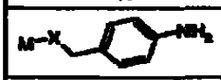
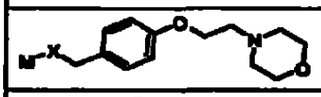
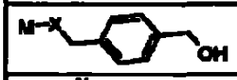
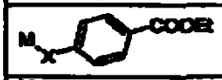
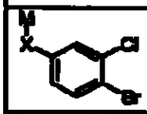
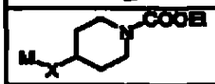
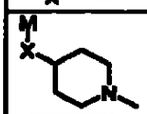
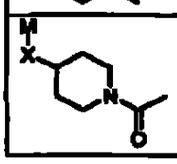
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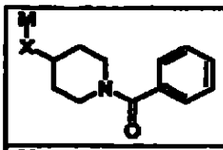
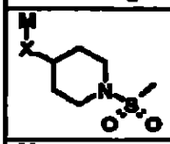
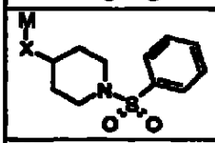
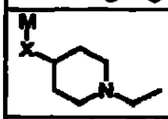
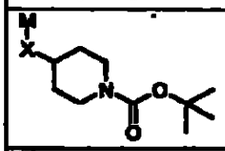
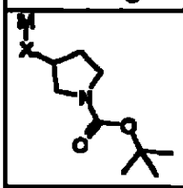
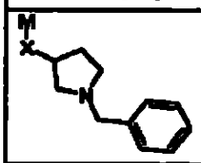
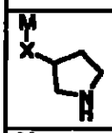
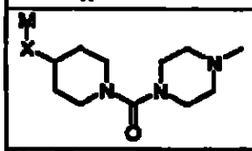
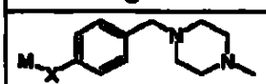
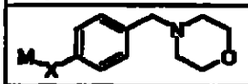
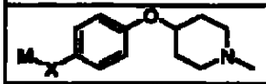
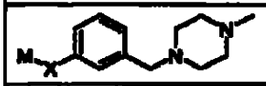
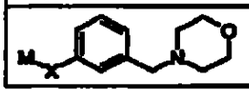
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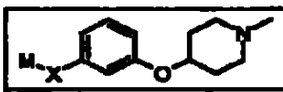
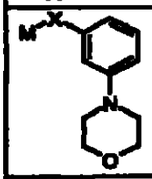
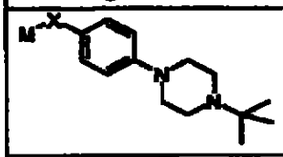
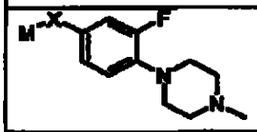
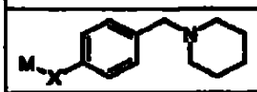
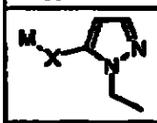
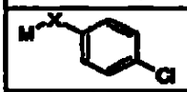
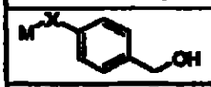
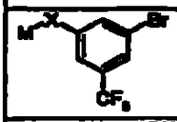
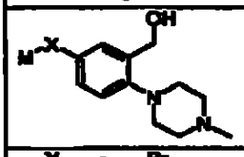
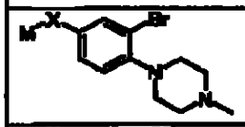
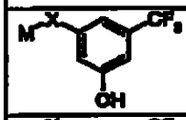
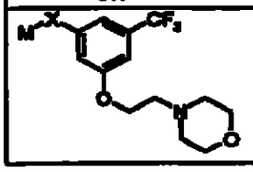
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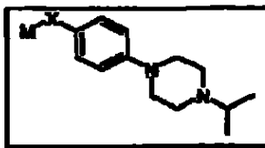
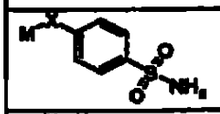
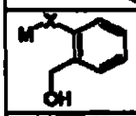
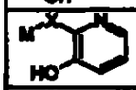
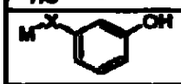
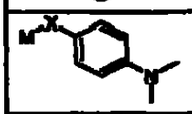
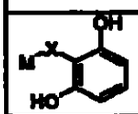
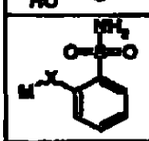
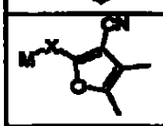
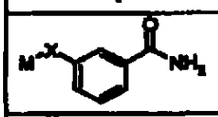
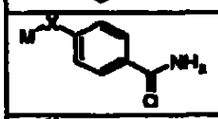
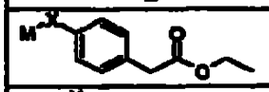
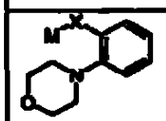
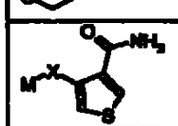
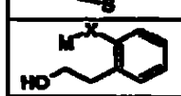
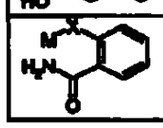
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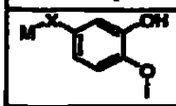
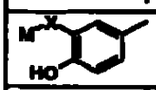
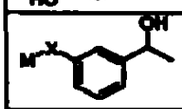
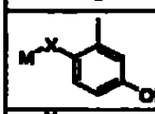
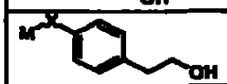
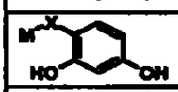
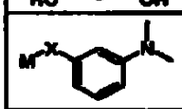
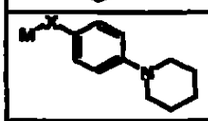
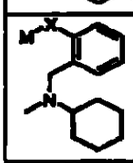
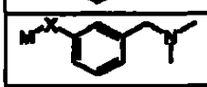
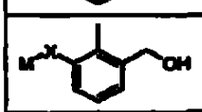
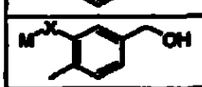
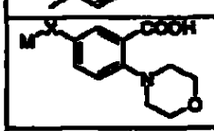
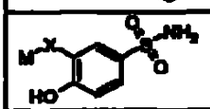
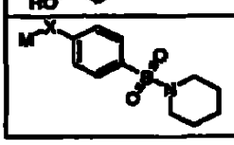
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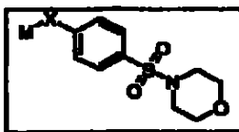
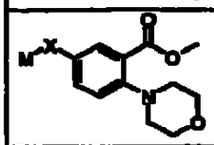
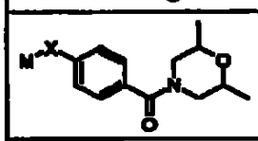
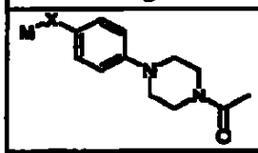
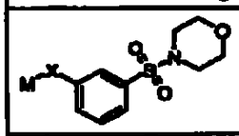
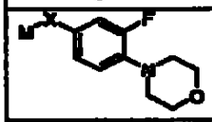
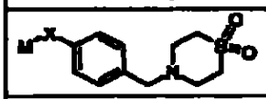
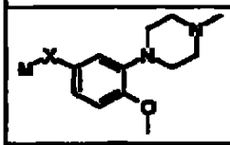
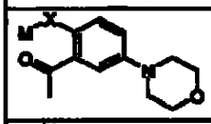
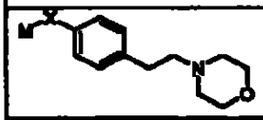
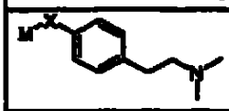
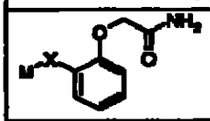
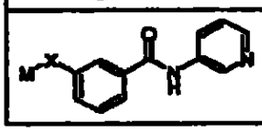
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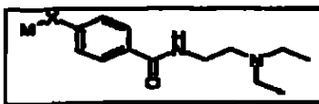
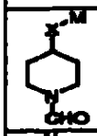
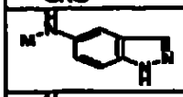
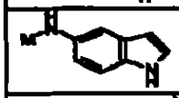
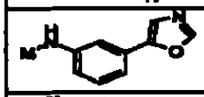
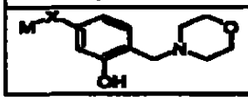
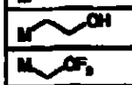
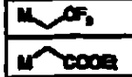
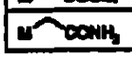
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Tabla II

TABLA DE LIGADORES X	
Fragmento	Código
-NH-M	X00
-CONH-M	X01
-NHCONH-M	X02.
-O-M	X03
-S-M	X04
$-SO_2-M$	X05
-M	X06

Tabla III

TABLA DE GRUPOS C	
Fragmento	Código
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M-Me	C01
M-tBu	C02
	C03
	C04
	C05
	C06
	C07

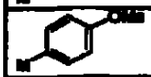
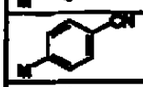
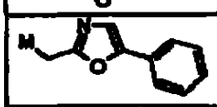
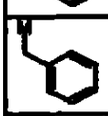
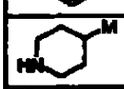
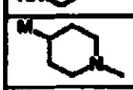
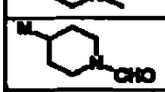
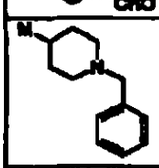
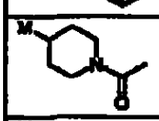
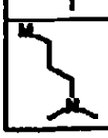
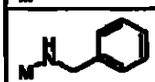
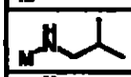
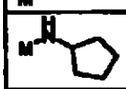
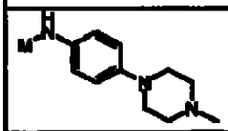
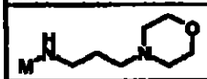
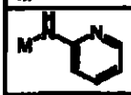
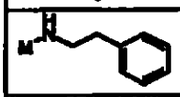
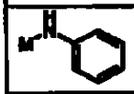
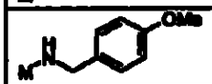
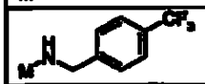
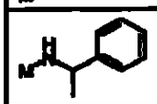
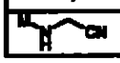
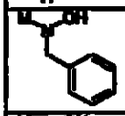
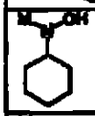
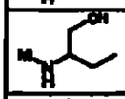
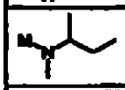
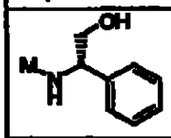
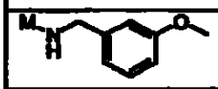
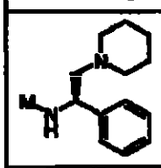
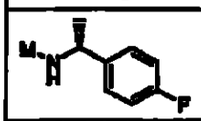
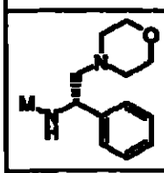
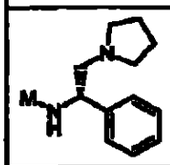
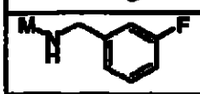
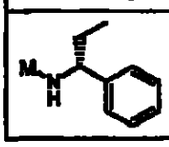
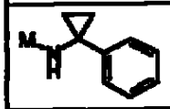
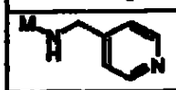
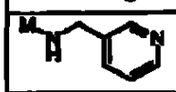
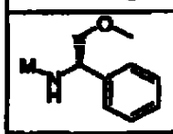
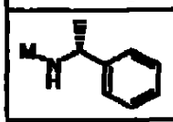
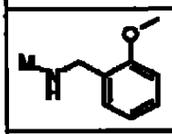
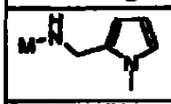
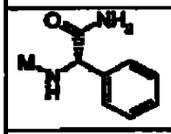
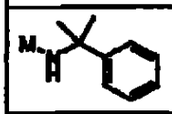
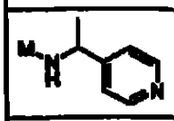
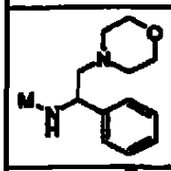
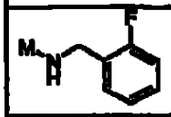
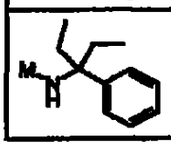
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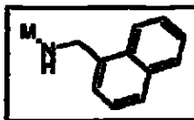
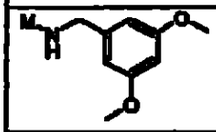
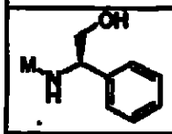
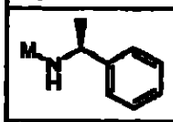
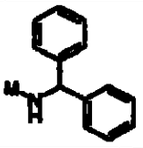
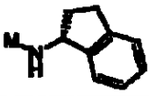
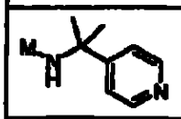
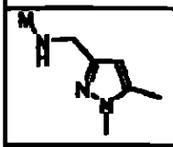
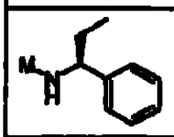
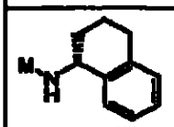
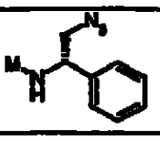
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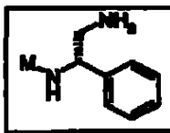
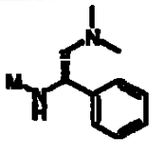
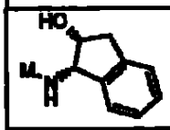
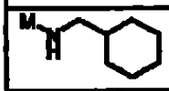
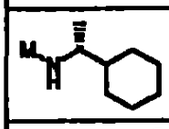
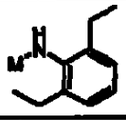
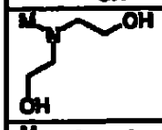
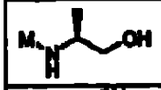
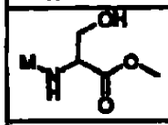
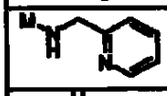
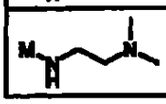
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M-OEt	D01
M-OH	D02

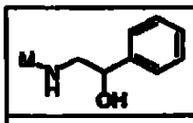
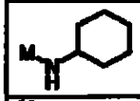
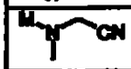
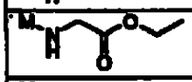
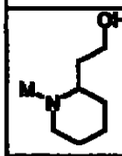
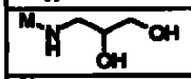
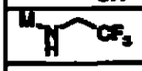
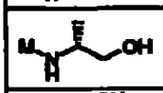
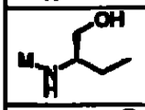
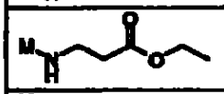
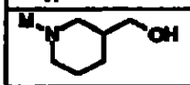
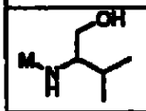
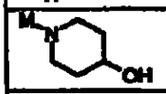
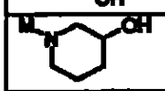
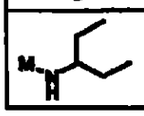
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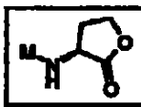
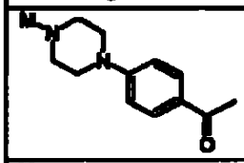
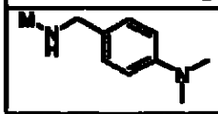
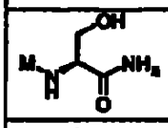
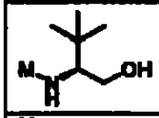
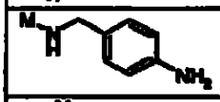
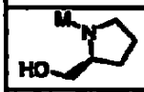
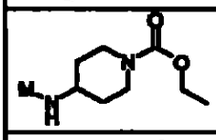
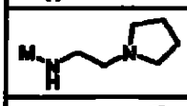
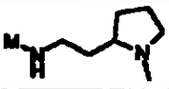
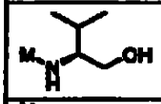
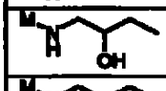
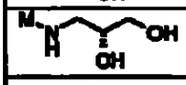
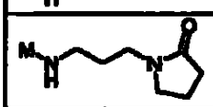
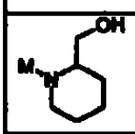
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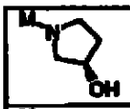
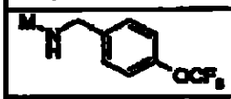
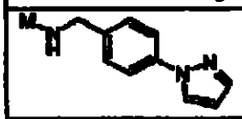
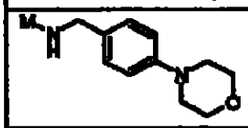
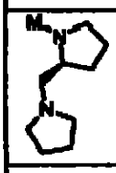
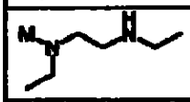
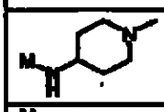
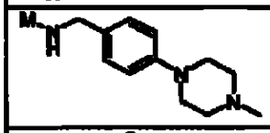
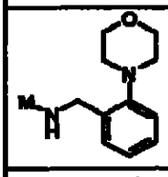
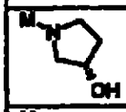
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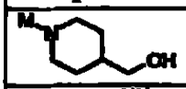
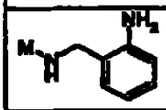
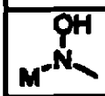
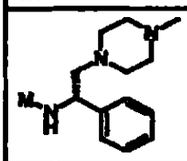
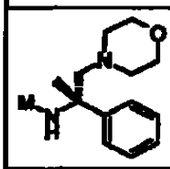
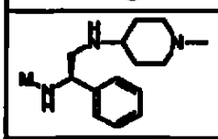
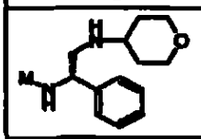
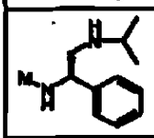
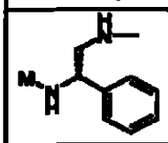
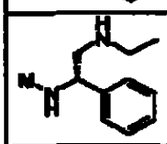
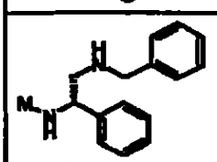
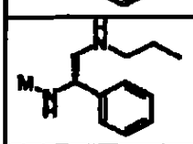
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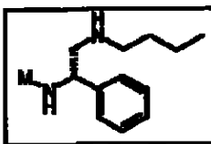
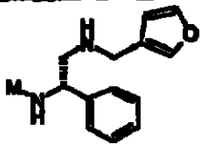
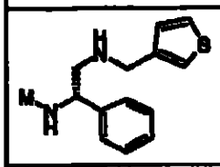
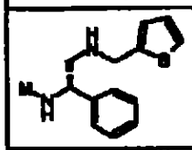
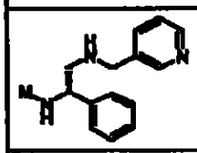
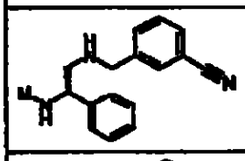
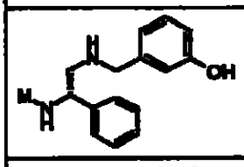
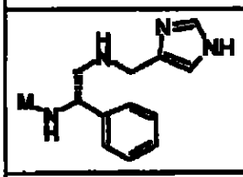
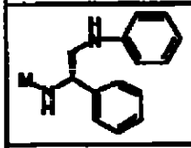
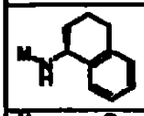
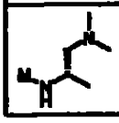
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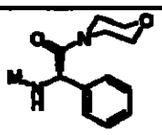
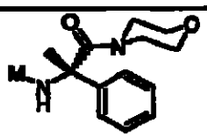
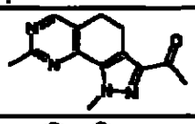
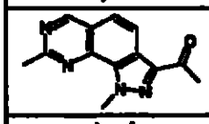
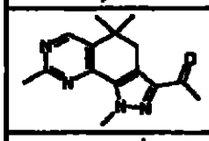
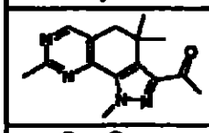
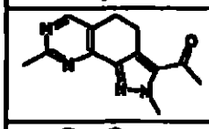
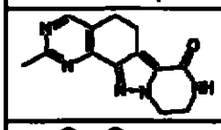
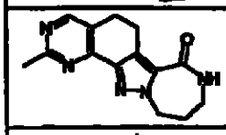
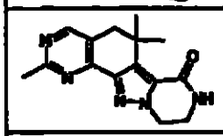
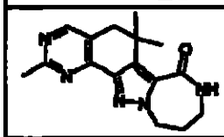
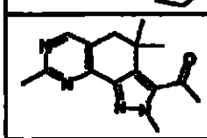
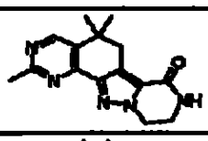
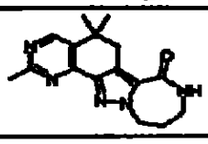
	D164
	D165

Tabla V

TABLA DE NÚCLEO M	
Estructura	Código
	M00
	M01
	M02
	M03
	M04
	M05
	M06
	M07
	M08
	M09

	M10
	M11

Los compuestos de la presente invención, preparados de acuerdo con los siguientes ejemplos, también se caracterizaron por ^{1H} RMN y/o por datos analíticos HPLC/MS; datos HPLC/MS fueron reconectados siguiendo unos de los métodos 1, 2 o 3.

Método 1 HPLC/MS

El equipamiento HPLC consistió de un sistema Waters 2790 HPLC equipado con un detector PDA 996 Waters y un espectrómetro de masa cuadrupolo Micromas mod. ZQ single, equipado con una fuente de iones de electrorociado (ESI). El control del instrumento, la adquisición de datos y el procesamiento de datos se suministro por el software Empower and MassLynx 4.0.

El HPLC fue llevado a cabo a 25°C a una proporción de flujo de 1 mL/min utilizando una columna RP18 Waters X Terra (4,6 x 50 mm, 3.5 µm). La fase A móvil fue de 5 mM de amortiguador de acetato de amonio (pH 5.5 con acido acético/acetonitrilo

95:5), y la fase B móvil fue H_2O/acetonitrilo (5:95): el gradiente fue de 10 a 90% de B en 8 minutos luego mantenido a 90% de 2 minutos. El volumen de inyección fue de 10 µl.

El espectrómetro de masa fue operado en un modo de ion positivo y negativo, el voltaje capilar fue configurado a 2.5 KV; la fuente de temperatura fue 120°C; el cono fue de 10 V; se configuro el rango de masa de exploración completa de 100 a 800 amu.

Método 2 HPLC/MS

El equipo HPLC consistió de un sistema Waters 2790 HPLC equipado con un detector 996 Waters PDA y un espectrómetro masas cuadrupolo mod. ZQ single, equipado con una fuente de Ion de electrorociado (ESI). El control de instrumentos, la adquisición de datos y el procesamiento de datos fue suministrado por el software Empower and MassLynx 4.0.

El HPLC fue llevado a cabo a 25°C a una proporción de flujo de 1 mL/min utilizando una columna RP18 Waters X Terra (3.0 x 30 mm, 3.5 µm). La fase A móvil fue de 5 mm de un amortiguados de acetato de amonio (pH 5.5 con acido acético/acetonitrilo 95:5), la fase B móvil fue de H_2O/acetonitrilo (5:95); el gradiente fue de 10 a 90% de B 4

minutos luego mantenida a 90% B 1 minuto. El volumen de inyección fue de 10 µl.

El espectrómetro de masa fue operado en modo de Ion positivo y en negativo, el voltaje capilar se estableció en 2.5 KV; la fuente de temperatura fue de 120°C, el cono fue de 10 V; se configuro el rango de masa de exploración completa de 100 a 800 amu.

Método 3 HPLC/MS

El espectro de masa fue registrado sobre un espectrómetro de masa de trampa de ion LCQ Finnigan utilizando la técnica de ionización de electrorociado (ESI) con detección de Ion positivo y negativo. El espectrómetro de masa esta directamente conectado al sistema SSP4000 HPLC (termoseparación), equipado con un automuestreador LcPal (CTC Analytics) y un detector UV 6000LP PDA (termoseparación). El control del instrumento, la adquisición de datos y el procesamiento fue desarrollado utilizando un software Xcalibur 1.2. El análisis HPLC fue llevado a cabo a temperatura ambiente y a una proporción de flujo 1 mL/min utilizando una columna RP C18 Waters ZorbaxSB C18 (4.6 x 50 mm; 1.8 µm).

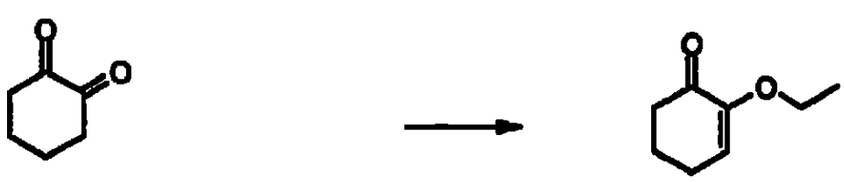
La fase A móvil fue 5 mM de amortiguador de acetato de amonio (pH 5.5 con acido acético): acetonitrilo 90:10, y la fase B móvil fue de 5 mM de amortiguador de acetato de amonio (pH 5.5 con acido acético): acetonitrilo 10:90, el gradiente fue de 0 a 100% B en 7 minutos y luego mantenido 100% B durante 2 minutos antes de reequilibrio. El tiempo total LC es de 12 minutos. El volumen de inyección fue 10 µl. La detección UV se desarrollo entre 215 y 400 nm.

Los iones fueron generados bajo las siguientes condiciones: voltaje de rociador ESI 4.0 kV, temperatura capilar calentada 255°C, el gas nitrógeno de cubierta con una presión de 5.0 Bar. Un modo de detección de exploración completa (de 50 a 1000 amu) se utilizo con un análisis MS/MS del Ion mas intenso (energía de colisión normalizada: 35%).

Detección UV: 215-400 nm.

Ejemplo 1

2-etoxiciclohex-2-en-1-ona

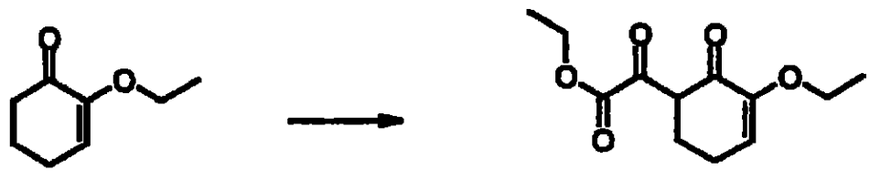


50 g (0.45 mol) de 1,2-diciclohexandione se disolvió en una mezcla de 1 L de tolueno 0.5 L de etanol, 10 g de acido p-toluenosulfonico se agregó y la solución se calentó a reflujo durante 2 días. (TCL cloroformo/metanol 6/1). El solvente fue luego evaporado, el residuo redisuelto con diclorometano y lavado con solución saturada de $NaHCO_3$. La capa orgánica se seco sobre Na_2SO_4 y se concentró. El crudo se purificó y se cromatografió sobre una columna de sílica gel al eluar con una mezcla de ciclohexano/acetato de etilo 98/2 (66% de rendimiento como un aceite).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, 3 H) 2.33-2.39 (m, 6 H) 3.67 (q, 2 H) 5.97 (t, 1 H).

Ejemplo 2

Etil (3-etoxi-2-oxocyclohex-3-en-1-il)(oxo)acetato



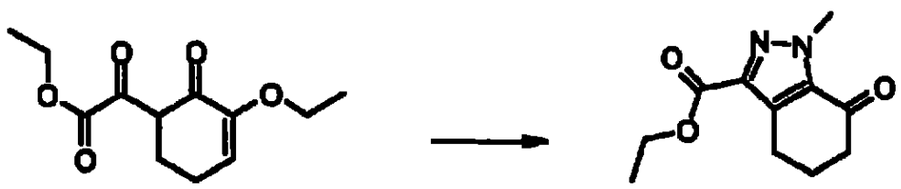
41.40 g (0.29 mol) de 2-etoxiciclohex-2-en-1-one fueron disueltos en 310 mL de dietil eter y 325 mL de 1M $liN(TMS)_2$ en tetrahidrofuerano fueron agregados gota a gota a -50°C. Después de 30 minutos a la misma temperatura, 44.2 mL de

dietiloxalato fueron también agregados bajo agitación. La solución se mantuvo a temperatura ambiente durante toda la noche (TLC cloroformo). 300 mL de agua fueron entonces agregados, el pH ajustado a 4-5 al agregar HCL 1 N y la solución resultante se extrajo con acetato de etilo. La capa orgánica se seco sobre Na_2SO_4 y se evaporó hasta sequedad. El crudo se purificó mediante cromatografías sobre una columna de sílica gel eluada mediante cloroformo (765 de rendimiento como un aceite).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H) 1.51 (t, 3 H) 2.06-2.58 (m, 4 H) 3.57 (m, 1 H) 3.86 (q, 2 H).4.38 (q, 2 H) 6.09 (m, 1 H).

Ejemplo 3

Etil 1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato



30 g (0.125 mol) de etil (3-etoxi-2-oxociclohex-3-en-1-il)(oxo)acetato se disolvieron en 150 mL de acido acetico glacial y se agregaron 6.5 mL de metilhidrazina. La mezcla de agitó a temperatura ambiente durante 6 horas. El solvente fue

entonces evaporado y el crudo redisuelto con agua, la solución se basificó con 30% de Na_2SO_4 y extraída con cloroformo. La capa orgánica fue entonces secada sobre Na_2SO_4 y concentrada. El residuo se cromatografió sobre una columna de sílica gel (eluyente: cloroformo) y cristalizada de una mezcla de n-hexano/dietil eter (TLC cloroformo; 63% rendimiento como un sólido blanco).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J* 6.89 Hz, 3 H) 1.51 (t, *J* 6.94 Hz, 3 H) 2.06-2.58 (m, 4 H) 3.57 (m, 1 H) 3.86 (q, *J* 6.83 Hz, 2 H).4.38 (q, *J* 6.94 Hz, 2 H) 6.09 (m, 1 H).

De acuerdo con el mismo método, pero empleando el derivado de hidrazina sustituido adecuado, se prepararon los siguientes compuestos:

Etil 1-tert-butil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, *J* 6.89 Hz, 3 H) 1.581 (s, 9 H) 2.30-2.93 (3m, 6 H) 4.18 (q, *J* 6.83 Hz, 2 H);

Etil 1-(2-hidroxietil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, *J* 7.20 Hz, 3 H) 1.9-2.9 (3m, 6 H) 3.7 (m, 2 H) 4.3 (q, *J* 7.20 Hz, 2 H).4.53 (t, *J* 5.85, 2 H) 4.77 (t, *J* 5.73, OH).

Etil 1-(2-etoxi-2-oxoetil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, *J* 7.20 Hz, 3 H) 1.29 (t, *J* 7.20 Hz, 3 H) 2.04 (m, 2 H); 2.52 (m, 2 H) 2.93 (q, *J* 6.10 Hz, 2 H).4.04 (q, *J* 7.07 Hz, 2 H) 4.37 (q, *J* 7.20 Hz, 2 H).5.26 (s, 1 H);

Etil 7-oxo-1-(2,2,2-trifluoroetil)-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 2.05 (m, 2 H) 2.57 (m, 2 H) 2.95 (m, 2 H) 4.2 (q, *J* 7.07 Hz, 2 H) 5.3 (2d, 2 H);

Etil 7-oxo-2-(2,2,2-trifluoroetil)-4,5,6,7-tetrahidro-2H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.08 Hz, 3 H) 2.05 (m, 2 H); 2.57 (t, *J* 7.44 Hz, 2 H).2.94 (m, 2 H) 4.30 (q, *J* 7.19 Hz, 2 H).5.46 (2d, 2 H);

Etil 7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J* 7.07 Hz, 3 H) 2.04 (m, 2 H); 2.51 (m, 2 H) 2.87 (t, *J* 6.10 Hz, 2 H).4.27 (q, *J* 7.11 Hz, 2 H) 14.39 (s, 1 H);

Etil 1-[4-(aminosulfonil)fenil]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J* 7.13 Hz, 3 H) 2.10-2.19 (m, 2 H); 2.57-2.63 (m, 2 H) 3.05 (t, *J* 6.10 Hz, 2 H).4.37 (q, *J* 7.07 Hz, 2 H) 7.54 (s, 2 H) 7.77 (d, *J* 8.78 Hz, 2 H) 7.96 (d, *J* 8.90 Hz, 2 H);

Etil 1-(4-metoxifenil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.05-2.17 (m, 2 H); 2.56 (dd, *J* 7.26, 5.55 Hz, 2 H).3.03 (t, *J* 6.10 Hz, 2 H) 3.85 (s, 3 H) 4.34 (q, *J* 7.07 Hz, 2 H) 7.05 (d, *J* 9.02 Hz, 2 H) 7.44 (d, *J* 9.02 Hz, 2 H);

Etil 1-(4-cianofenil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J* 7.07 Hz, 3 H) 2.09-2.19 (m, 2 H); 2.60 (dd, *J* 7.32, 5.49 Hz, 2 H).3.04 (t, *J* 6.16 Hz, 2 H) 4.36 (q, *J* 7.11 Hz, 2 H) 7.80 (d, *J* 8.90 Hz, 2 H) 8.03 (d, *J* 8.78 Hz, 2 H);

Etil 7-oxo-1-piridin-2-il-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J* 7.13 Hz, 3 H) 2.10-2.21 (m, 2 H); 2.58 (dd, *J* 7.32, 5.61 Hz, 2 H).3.05 (t, *J* 6.16 Hz, 2 H) 4.36 (q, *J* 7.07 Hz, 2 H) 7.61 (ddd, *J* 7.41, 4.73, 1.04 Hz, 1 H) 7.64 (dt, *J* 7.93, 0.98 Hz, 1 H) 8.07 (td, *J* 7.74, 1.83 Hz, 1 H) 8.57 (ddd, *J* 4.79, 1.86, 0.79 Hz, 1 H);

Etil 7-oxo-1-fenil-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, 3H, J 7.08) 2.08 (m, 2 H); 2.54 (m, 2 H) 4.30 (q, 2H, J 7.08) 7.49 (m, 5 H);

Etil 1-benzil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

Etil 1-(1-metilpiperidin-4-il)-7-oxo-4,5,6,7-tetrahidro-1 H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.07 Hz, 3 H) 1.84-2.11 (m, 6 H); 2.28 (s, 3 H) 2.48-2.53 (m, 2 H) 2.91-3.00 (m, 2 H) 2.94 (t, *J* 6.16 Hz, 2 H) 4.32 (q, *J* 7.15 Hz, 2 H) 4.93-5.11 (m, 1 H);

(El derivado hidrazino que se empleo no se encuentra comercialmente disponible (CAS numero 53242-78-7) y fue sintetizado, como se describe en la literatura: WO 02/085906).

Etil 7-oxo-1-piperidin-4-il-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

(El derivado hidrazino que se empleo no se encuentra disponible comercialmente y se sintetizó como se describe en la literatura: DE 3634942 A1).

Etil 1-(1-benzilpiperidin-4-il)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.07 H) 3.34 (s, 2 H) 4.31 (q, 2 H, J 7.07 Hz) 5.06 (m, 1 H) 7.35 (m, 5 H);

Etil 1-(1-acetilpiperidin-4-il)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

(El derivado hidrazino que se empleo no se encuentra comercialmente disponible y por lo tanto se sintetizó como se reporto en el ejemplo 69).

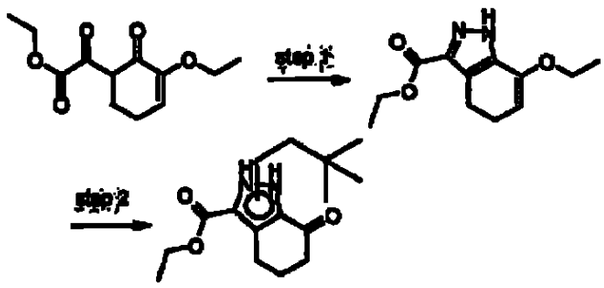
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (bs, 3 H) 2.59 (m, 1 H) 2.95 (m, 1 H) 3.29 (m, 1 H) 3.94 (m, 1 H) 4.30 (m, 2 H) 4.48 (m, 1 H) 5.29 (m, 1 H);

Etil 1-(2-dimetilaminoetil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

Etil 1-(2-dimetilaminopropil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

Ejemplo 4

Etil 1(2)-(3,3-dimetilbutil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato



Etapa 1. Etil 7-etoxi-4,5-dihidro-1 H-indazole-3-carboxilato

1.2 g (5 mmol) de etil (3-etoxi-2-oxociclohex-3-en-1-il)(oxo) acetato se disolvió en 20 mL de etanol y 25 mL (5.2 mmol) de hidrato de hidrazina 98% se agregó gota a gota. La solución se agito a temperatura ambiente durante 5 horas, luego se calentó a 60°C durante 5 horas adicionales. El solvente se removió in vacuo y el residuo se tomo con dietil eter y el precipitado resultante se recolecto mediante filtración dando 0.8 g del compuesto del titulo, que se empleo en la siguiente etapa sin purificación adicional.

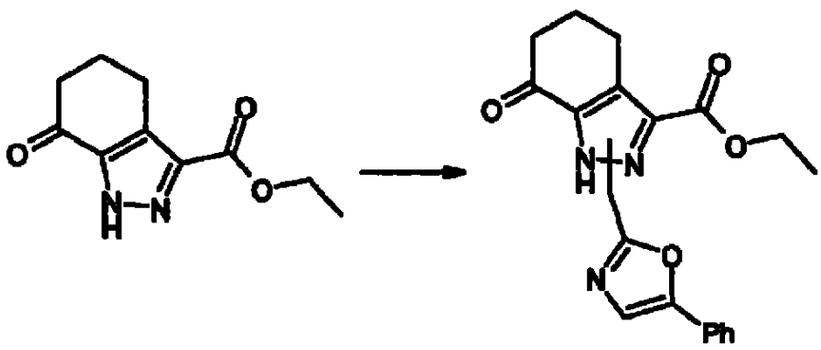
Etapa 2. Etil 1(2)-(3,3-dimetilbutil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

0.28 g (1.17 mmol) de etil 7-etoxi-4,5-dihidro-1H-indazole-3-carboxilato se disolvió en 12 mL de dimetilformamida seca y se agregó 0.25 g (1.40 mmol) de 3,3-dimetilbutil

metanosulfonato. La solución resultante se trato con 0.06 g (1.40 mmol) de hidruro de sodio 60% en aceite mineral y la mezcla de reacción se agito a 65°C durante 4 horas. Se agregó agua a la reacción y la solución se extrajo con acetato de etilo. El solvente se evaporó in vacuo y el residuo se redisolvio con 10 mL de metanol. Fueron agregadas entonces pocas gotas de HCL 1 N y después de 3 horas de reacción fue particionado entre agua y acetato de etilo, dando un crudo que, después de secar sobre Na_2SO_4, se purificó mediante cromatografia sobre columna de silica gel (eluyente hexano/etil acetato 95/5) (75% de rendimiento).

Ejemplo 5

Etil 7-oxo-1(2)-[(5-fenil-1,3-oxazol-2-il)metil]-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato



900 mg (4.3 mmol) de etil 7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato se disolvieron en 26 mL de DMF y 712 mg (5.16 mmol) de K_2CO_3 y fueron agregados 995 mg (5.16 mmol) de 2-(clorometil)-5-fenil-1,3-oxazol, la mezcla de reacción se agito a temperatura ambiente durante 5 horas y luego el solvente se removió bajo vacío el residuo se disolvió en diclorometano y se lavo con agua. La capa orgánica se seco sobre Na_2SO_4 y se evaporó hasta sequedad. Mediante cromatografía, fueron recuperados 405 mg (30% de rendimiento) de dos regioisómeros.

Etil 7-oxo-1-[(5-fenil-1,3-oxazol-2-il)metil]-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

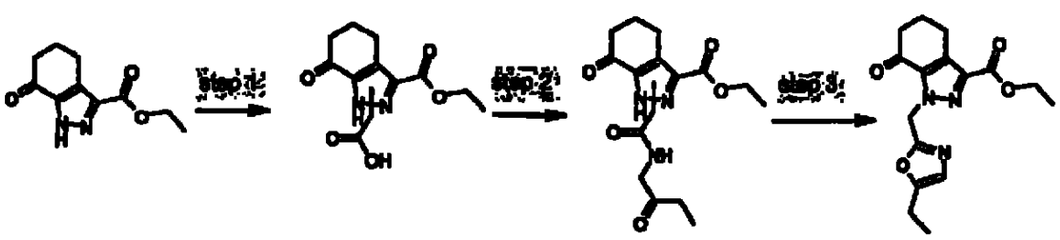
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, 3 H) 2.09 (m, 2 H) 2.59 (m, 2 H) 2.97 (m, 2 H) 4.31 (q, 2 H) 6.04 (s, 2 H) 7.39 (m, 1 H) 7.49 (m, 2 H) 7.63 (s, 1 H) 7.66 (m, 2 H);

Etil 7-oxo-2-[(5-fenil-1,3-oxazol-2-il)metil]-4,5,6,7-tetrahidro-2H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.09 (m, 2 H) 2.60 (m, 2 H) 2.99 (m, 2 H) 4.31 (q, 2 H) 5.98 (s, 2 H) 7.39 (m, 1 H) 7.49 (m, 2 H) 7.62 (s, 1 H) 7.66 (m, 2 H).

Ejemplo 6

Etil 1-[(5-etil-1,3-oxazol-2-il)metil]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato



Etapa 1. ácido [3-(etoxicarbonil)-7-oxo-4,5,6,7-tetrahidro-1H-indazol-1(2)-il] acetico

1 g (4.8 mmol) de etil 7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato se disolvió en 30 mL de DMF seco y se trato con 1.59 g (11.52 mmol) de K_2CO_3 y 800 mg (5.76 mmol) de acido bromoacético a temperatura ambiente. Después de calentar a 80°C durante toda la noche la mezcla se enfrió y el solvente se removió bajo vacío. El crudo fue disuelto en agua y neutralizado con HCL 37%. Tres extracciones con diclorometano lograron 1.7g del crudo que fue purificado mediante cromatografía de destello (diclorometano eluyente) produciendo 783 mg (61%) del producto como mezcla de regioisómero.

Etapa 2. Etil 7-oxo-1(2)-{2-oxo-2-[2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

743 mg (2.79 mmol) de acido [3-(etoxicarbonil)-7-oxo-4,5,6,7-tetrahidro-1H-indazol-1(2)-il]acetico como mezcla de isomeros fueron disueltos en 28 mL de DMF y 2.18 g (4.18 mmol) de benzotriazol-1-iloxitris(pirrolidino)fosfonio hexafluorofosfato (PyBOP), 690 mg (5.58 mmol) de clorhidrato de 1-aminobutan-2-one y se agregaron 2.4 mL (13.95 mmol) de N-etil-N,N-diisopropilamina. Después de 2 horas el solvente se evaporó en vacío, el crudo se disolvió en diclorometano y se lavo con $NaHCO_3$. Saturado, agua salubre y agua. La purificación mediante cromatografía de destello (hexano eluyente/etilacetato 8/2) produjo 511 mg de etil 7-oxo-1-{2-oxo-2-[(2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato y 20 mg de etil 7-oxo-2-{2-oxo-2-[(2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilate (57% de rendimiento total).

etil 7-oxo-1-{2-oxo-2-[(2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 (t, 3 H) 1.32 (m, 2 H) 2.44 (q, 2 H) 2.52 (t, 2 H) 2.96 (t, 2 H) 3.98 (d, 2 H) 4.31 (q, 2 H) 5.26 (s, 2 H) 8.44 (t, 1 H);

etil 7-oxo-2-{2-oxo-2-[(2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.94 (t, 3 H) 1.31 (t, 3 H) 2.08 (m, 2 H) 2.44 (q, 2 H) 2.53 (t, 2 H) 2.94 (t, 2 H) 3.99 (d, 2 H) 4.29 (q, 2 H) 5.32 (s, 2 H) 8.48 (t, 1 H).

Etapa 3. Etil 1-[(5-etil-1,3-oxazol-2-il)metil]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato

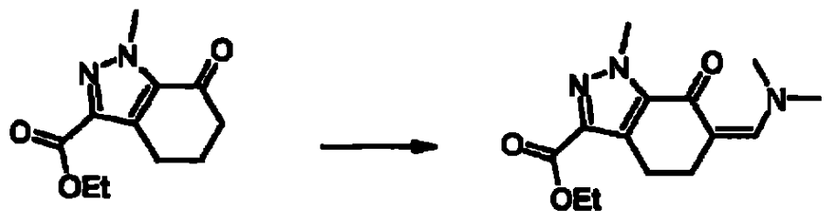
Una solución de 506 mg (1.51 mmol) de etil 7-oxo-1-{2-oxo-2-[(2-oxobutil)amino]etil}-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato en tolueno (45 mL) se trataron con 0.422 mL (4.53 mmol) de triclururo fosfórico y calentados a 90°C por 15 horas. La mezcla se enfrió a temperatura ambiente, se vertió en hielo y se neutralizo con NaOH 5N, la fase acuosa se extrajo con diclorometano y la capa orgánica logro 425 mg de crudo que se purificó sobre sílica gel (eluyente hexano/etilacetato 7/3). 285 mg del compuesto de titulo fueron así aislados (60%de rendimiento)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, 3 H) 1.32 (t, 3 H) 2.08 (m, 2 H) 2.63 (m, 4 H) 2.97 (t, 2 H) 4.31 (q, 2 H) 5.84 (s, 2 H) 6.79 (s, 1 H).

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Ejemplo 7

Etil 6-[(dimetilamino)metileno]-1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato



16 g (0.07 mol) de etil 1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato se disolvieron en 100 mL de dimetilformamida y se agregaron 32 ml de dimetilformamida diterbutil acetato. La mezcla se agito 60°C durante 8 horas. El solvente luego se evaporó en vacuo y el producto fue cristalizado de etanol (90% de rendimiento).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72-2.95 (m, 4 H) 3.04-3.14 (m, 6 H) 4.10 (s, 3 H) 4.24 (q, *J* 7.20 Hz, 2 H) 7.46 (m, 1 H).

Al trabajar de acuerdo con el mismo método se prepararon los siguientes compuestos:

Etil 1-tert-butil-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 6-[(dimetilamino)metileno]-1-(2-hidroxietil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (t, *J* 6.34 Hz, 2 H) 2.88 (t, *J* 6.21, 2 H).3.70 (m, 2 H) 4.24 (q, *J* 7.07 Hz, 3 H) 4.58 (t, *J* 5.97 Hz, 2 H) 4.79 (bs, OH) 7.47 (bs, 1 H);

Etil 6-[(dimetilamino)metileno]-1-(2-etoxi-2-oxoetil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J* 7.07 Hz, 3 H) 1.28 (t, *J* 7.13 Hz, 3H).2.86 (m, 4 H) 3.10 (s, 6 H) 4.10 (q, *J* 7.11 Hz, 2 H) 4.26 (q, *J* 7.11 Hz, 2 H) 5.33 (s, 2 H) 7.43 (s, 1 H);

Etil 1-[4-(aminosulfonil)fenil]-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil -6-[(dimetilamino)metileno]-1-(4-metoxifenil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.07 Hz, 3 H) 2.87-2.93 (m, 2 H).2.95-3.00 (m, 2 H) 3.12 (s, 6 H) 3.83 (s, 3 H) 4.32 (q, *J* 7.07 Hz, 2 H) 7.00 (d, *J* 9.02 Hz, 2 H) 7.39 (d, *J* 9.02 Hz, 2 H) 7.42 (s, 1 H);

Etil 1-(4-cianofenil)-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 2.88-2.94 (m, 2 H).2.97-3.03 (m, 2 H) 3.14 (s, 6 H) 4.34 (q, *J* 7.15 Hz, 2 H) 7.48 (s, 1 H) 7.73 (d, *J* 8.90 Hz, 2 H) 7.96 (d, *J* 8.78 Hz, 2 H);

Etil -6-[(dimetilamino)metileno]-7-oxo-1-piridin-2-il-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.87-2.93 (m, 2 H).3.00 (t, *J* 6.71 Hz, 2 H) 3.13 (s, 6 H) 4.33 (q, *J* 7.07 Hz, 2 H) 7.40 (s, 1 H) 7.54;(ddd, *J* 7.47, 4.79, 1.04 Hz, 1 H) 7.56 (dt, *J* 8.02, 0.93 Hz, 1 H) 7.99-8.04 (m, 1 H) 8.52 (ddd, *J* 4.82, 1.89, 0.85 Hz, 1 H)

Etil 6-(dimetilamino)metileno-1-(3,3.dimetilaminobutil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 6-(dimetilamino)metileno-2-(3,3.dimetilaminobutil)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 6-[(dimetilamino)metileno]-7-oxo-1-(2,2,2-trifluoroetil)-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.88 (2m, 4 H).3.10 (s, 6 H) 4.33 (q, *J* 7.07 Hz, 2 H) 5.45 (q, *J* 8.90 Hz, 2 H) 7.50 (bs, 1 H);

Etil 6-[(dimetilamino)metileno]-7-oxo-2-(2,2,2-trifluoroetil)-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (t, *J* 7.07 Hz, 3 H) 2.82 (s, 3 H).4.29 (q, *J* 7.07 Hz, 2 H) 5.57 (q, *J* 9.02 Hz, 2 H) 7.53 (bs, 1 H);

Etil 6-[(dimetilamino)metileno]-7-oxo-1-fenil-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 1-benzil-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 6-[(dimetilamino)metileno]-1-(1-metilpiperidin-4-il)7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 6-[(dimetilamino)metileno]-7-oxo-1-piperidin-4-il-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 1-(1-benzilpiperidin-4-il)-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, *J* 7.07 Hz, 3 H) 1.76-2.15 (m, 4 H).2.79-3.01 (m, 4 H) 3.13 (s, 6 H) 3.24-3.64 (m, 6 H) 4.29 (q, *J* 7.07 Hz, 2 H) 5.30 (dd, *J* 17.01, 7.26 Hz, 1 H) 7.14-7.40 (m, 6 H).

Etil 1-(1-acetilpiperidina-4-il)-6-[(dimetilamino)metileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

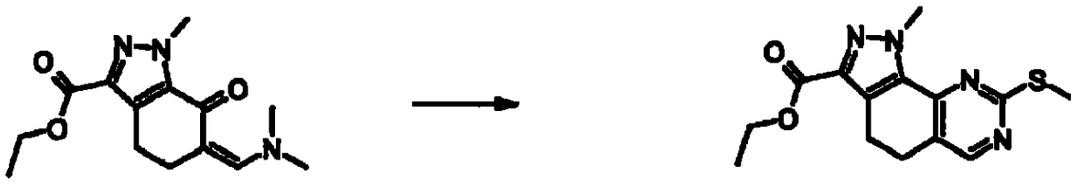
Etil 6-[(dimetilamino)metileno]-1-(1-formilpiperidina-4-il)-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 1-(2-dimetilaminoetil)metileno)-6-dimetilaminometileno-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Etil 1-(2-dimetilaminopropil)-6-dimetilaminometileno]-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato;

Ejemplo 8

Etil 1-metil-8-(metiltio)-4,5,-dihidro-1H-pirazolo[4,3-h]quinazoline -3-carboxilato [B67-X04-M00(C01)-D01]



9 g (69 mmol) de etil-6-[(dimetilamino) metileno]-1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazole-3-carboxilato se disolvieron en 350 mL de dimetilformamida anhidra y 13.4 g de acetato de potasio anhidro (138 mmol) y 19.18 g (19 mmol) y se agregaron 19.18 g (69 mmol) de sulfato de metilisotiourea. La mezcla se mantuvo a 90°C bajo agitación durante 8 horas. El solvente fue luego evaporado, el residuo redisuelto con diclorometano y lavado con agua. La capa orgánica se seco sobre Na_2SO_4 y se evaporó. El crudo fue finalmente triturado con dietileter y recolectado mediante filtración para dar 15.5 g (74% de rendimiento) del compuesto del titulo.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.54 (s, 3 H).2.84-3.00 (m, 4 H) 4.26 (q, *J* 7.07 Hz, 2 H) 4.31 (s, 3 H) 8.53 (m, 1 H).

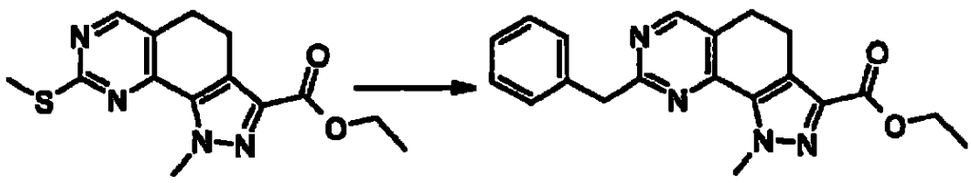
Luego el mismo método pero empleando un derivado de isotiurea sustituida adecuada, fueron preparados los siguientes compuestos:

Etil 8-(benziltio)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazoline -3-carboxilato [B04-X04-M00(C01)-D01];

Etil 1-metil-8-(feniltio)-4,5,-dihidro-1H-pirazolo[4,3-h]quinazoline -3-carboxilato [B04-X04-M00(C01)-D01]

Ejemplo 9

Etil 8-benzil-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazoline -3-carboxilato [B04-X06-M00(C01)-D01]



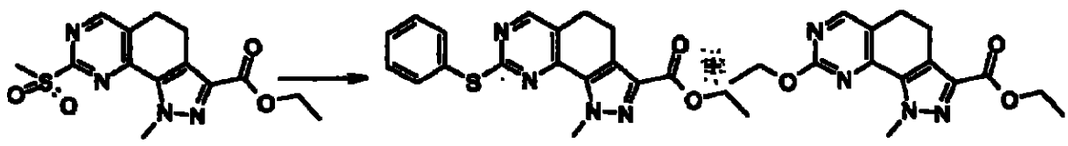
Bajo una atmósfera de nitrógeno, se agregaron 0.5 M de solución de bromuro de benzilzinc en THF (3.11 mL, 1.556 mmol) a una mezcla de etil 1-metil-8-(metiltio)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato (237 mg, 0.778 mmol) y $Pd(PPh_3)_4$ (9mg, 0.0078 mmol, 1%). Después de 20 horas de calentar a 60°C bajo nitrógeno, la mezcla fue enfriada a temperatura ambiente, agitada con bicarbonato de sodio acuoso

y etil acetato y luego filtrada. La fase orgánica fue entonces separada y la fase acuosa se extrajo dos veces con acetato de etilo. La fase orgánica combinada se seco sobre Na_2SO_4, se evaporó y el crudo fue purificado sobre sílica gel (eluyente de diclorometano/metanol 97/3). 20 mg del compuesto del titulo se aislaron.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.99 (m, 4 H).4.23 (s, 2 H) 4.27 (m, 5 H) 7.23 (m, 1 H) 7.32 (m, 2 H) 7.36 (m, 2 H) 8.66 (s, 1 H).

Ejemplo 10

Etil 1-metil-8-(feniltio)-4,5-dihidro-1H-pirazolo[4,3-h]quinazoline -3-carboxilato [B04-X04-M00(C01)-D01]



A una suspensión agitada de etil 1-metil-8-(metilsulfonil)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato (46 mg, 0.137 mmol) y feniltiol (16 µl, 17 mg, 0.15 mmol) en etanol (1 mL), se agregó hidróxido de sodio 1*N* (150 µl, 0.15 mmol) a temperatura ambiente bajo una atmósfera de argón.

Después la mezcla se agito durante 3 días, se agregó acido clorhídrico 1*N* (150 µl, 0.15 mmol) y el solvente se removió bajo vacío. Mediante cromatografía sobre sílica gel (eluyente: diclorometano/metanol 97/3), 13 mg de etil 1-metil-8-(feniltio)-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3-carboxilato y 10 mg de etil 8-etoxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato fueron aislados.

B04-X04-M00(C01)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, 3 H) 2.86 (t, 2 H).2.93 (t, 2 H) 3.68 (s, 3 H) 4.25 (q, 2 H) 7.48 (m, 3 H) 7.64 (m, 2 H) 8.53 (s, 1 H).;

B04-X04-M00(C01)-D01

B03-X03-M00(C01)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 1.38 (t, 3 H).2.91 (t, 2 H) 3.01 (t, 2 H) 4.33 (m, 5 H) 4.41 (q, 2 H).

Ejemplo 11

1-metil-8-(metiltio)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxamida [B67-X04-M00(C01)-D03]

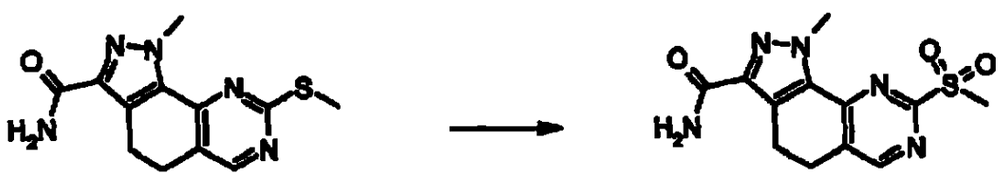
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13.00 g (0.043 mol) de etil 1-metil-8-(metiltio)-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3-carboxilato se suspendieron en una mezcla de 200 mL de metanol, 200 mL de dimetilformamida y 200 mL de hidrato de amonio 30%. La mezcla fue agitada a 65°C en una botella cerrada durante aproximadamente 8 horas. El solvente fue entonces evaporado hasta sequedad, el residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4 y se evaporó. El crudo se purificó mediante cromatografías sobre una columna de sílica gel eluada mediante una mezcla de ciclohexano/acetato de etilo, dando 6.16 g (52% de rendimiento) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.54 (s, 3 H) 2.75-3.05 (m, 4 H) 4.28 (s, 3 H) 7.47 (bs, 2 H) 8.51 (m, 1 H).

Ejemplo 12

1-metil-8-(metilsulfonil)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxamida [B67-X05-M00(C01)-D03]



6,00 g (0.022 mol) de 1-metil-8-(metiltio)-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3-carboxamida se disolvieron en 1000 mL de dimetilformamida y se agregaron 40.18 g de oxono. La mezcla se agitó 16 horas a temperatura ambiente. Fueron agregados entonces agua y acetato de etilo y separadas las capas. La capa orgánica se secó finalmente sobre Na_2SO_4 y se evaporó. El residuo fue triturado con dietileter y 5.40 g (80% de rendimiento) del compuesto del título fueron recolectados mediante filtración.

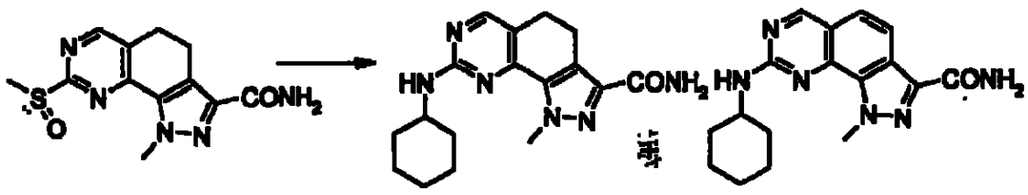
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (m, 4 H) 3.43 (s, 3 H) 4.29 (s, 3 H) 7.45 (bs, 2 H) 8.91 (m, 1 H).

Al trabajar de pronto con esta metodología se preparó el siguiente compuesto:

Etil 1-metil-8-(metilsulforil)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B67-X05-M00(C01)-D03]

Ejemplo 13

8-(ciclohexilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxamida [B27-X00-M00(C01)-D03] **y 8-(ciclohexilamino)-1-metil-1H-pirazolo[4,3-h]quinazolino-3-carboxamida**[B27-X00-M01(C01)-D03]



1.5 g de 1-metil-8-(metilsulfonil)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxamida fueron disueltos en 100 mL de dimetilsulfoxido seco y se agregaron 1.15 mL de ciclohexilamina. Después de 16 horas a 80°C bajo nitrógeno el solvente se evaporó y se redujo la presión. El residuo fue entonces redisuelto con diclorometano y y lavado con agua. La capa orgánica fue secada sobre Na_2SO_4 y evaporada hasta sequedad. Mediante cromatografía sobre una columna de sílica gel (eluante diclorometano/acetona 9/1) 300 mg de 8-(ciclohexilamino)-1-metil-1H-pirazolo[4,3-h]quinazolino-3-carboxamida y 200 mg de 8-(ciclohexilamino)-1-metil-4,5-dihidro de 1H-pirazolo[4,3-h]quinazolino-3-carboxamida y fueron obtenidos (30% de rendimiento total).

B27-X00-M00-(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (m, 10 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.69 (m, 1 H) 4.31 (m, 3 H) 6.94 (d, *J* 6.58 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H);

B27-X00-M01-(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63 (m, 10 H) 3.88 (m, 1 H) 4.66 (s, 3 H) 7.40 (s, 1 H) 7.47 (d, *J* 8.66 Hz, 1 H) 7.59 (s, 1 H) 7.74 (s, 1 H) 7.87 (d, *J* 8.66 Hz, 1 H) 9.13 (s, 1 H)

Al trabajar de acuerdo con esta metodología, y al tomar en cuanta que cuando la amina está disponible como una sal, cantidades estequimétricas de carbonato de potasio fueron empleadas, los siguientes compuestos fueron preparados como se codificó en la tabla 6:

B76-X06-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 6 H) 2.75 (m, 2 H) 2.96 (m, 2 H) 3.76 (m, 4 H) 4.29 (s, 3 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.29 (s, 1 H)
B23-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 2.21 (s, 6 H) 2.46 (m, , 2 H) 2.74 (m, 2 H) 2.95 (m, , 2 H) 3.41 (m, 2 H) 4.32 (s, 3 H) 6.90 (t, *J* 5.73 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B24-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 (m, 4 H); 2.49 (m, 4 H); 2.95 and 2.61 (2m, 4 H); 3.40 (m, 2 H); 4.32 (s, 3 H); 6.95 (bs, NH); 7.2-7.4 (2s, 2 H); 8.21 (s, 1 H).
B25-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 6 H) 2.52 (m, 6 H) 2.70 (m, 2 H,) 2.95 (m, 2 H,) 3.42 (m, 2 H) 4.32 (s, 3 H) 7.2-7.4 (2s, 2 H) 8.21 (s, 1 H).
B26-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37-2.54 (m, 6 H) 2.74 (m, 2 H,) 2.95 (m, 2 H.) 3.45 (m, 2 H) 3.59 (m, 4 H) 4.32 (s, 3 H) 6.93 (bs, NH) 8.22 (s, 1 H).
B28-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (m, 11 H) 2.72 (m, 2 H) 2.94 (m, 2 H,) 3.16 (m, 2 H) 4.31 (s, 3 H) 7.14-7.49 (3bs, 3 H) 8.19 (s, 1 H).
B29-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 (m, 3 H) 2.60-3.20 (m, 10H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.88 (m, 1 H) 4.31 (s, 3 H) 6.88 (bs, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.22 (s, 1 H).

B30-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (m, 2 H) 3.07 (m, 2 H) 4.34 (s, 3 H) 6.60 (m, 2 H) 7.44 (m, 2 H) 7.32 (s, 1 H) 8.71 (s, 1 H).
B31-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.62 (d, *J* 6.10 Hz, 2 H) 7.23 (m, 2 H) 7.34 (m, 1 H) 7.41 (s, 1 H) 7.73 (m, 2 H) 8.24 (s, 1 H) 8.50 (m, 1 H).
B32-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (m, 4 H) 4.17 (s, 3 H) 4.56 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.34 (dd, *J* 7.87, 4.69 Hz, 1 H) 7.42 (s, 1 H) 7.74 (m, 1 H) 7.74 (dt, *J* 7.68, 1.83 Hz, 1 H) 8.24 (s, 1 H) 8.44 (dd, *J* 4.76, 1.46 Hz, 1 H) 8.57 (d, *J* 1.83 Hz, 1 H)
B33-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 4.55 (d, J 6.22 Hz, 2 H) 7.22 (s, 1 H) 7.32 (m, 2 H) 7.41 (s, 1 H) 7.78 (bs, 1 H) 8.24 (s, 1 H) 8.49 (m, 2 H).
B34-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.94 (m, 2 H) 4.62 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.54-7.76 (2m, 4 H) 7.82 (bs. 1 H) 8.24 (s, 1 H).
B35-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.23 (s, 3 H) 4.44 (d, *J* 6.22 Hz, 2 H) 5.97 (s, 2 H) 6.83 (m, 2 H) 6.91 (s, 1 H) 7.23 (s, 1 H);7.42 (s, 1 H) 7.63 (bs, 1 H) 8.23 (s, 1 H).

B37-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.73 (m, 2 H) 1.93 (m, 2 H) 2.22 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.34 (m, 4 H) 4.32 (s, 3 H) 7.09 (bs, 1 H) 7.22 (s, 1 H) 7.43 (s, 1 H) 8.22 (s, 1 H).
B38-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.81 (t, *J* 7.38 Hz, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.54 (m, 2 H) 4.32 (s, 3 H) 6.86 (s, 1 H) 7.16 (t, *J* 5.55 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.61 (s, 1 H) 8.22 (s, 1 H) 12.00 (s, 1 H)
B39-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (m, 2 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.33 (m, 4 H) 4.25 (s, 3 H) 6.99 (s, 1 H) 7.27 (m, 3 H) 7.24 (s, 3 H) 7.43 (s, 1 H) 7.80 (s, 1 H) 8.22 (s, 1 H).
B40-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.44 (m, *J* 4.39 Hz, 4 H) 2.83 (m, 4 H) 3.10 (m, 4 H) 4.20 (s, 3 H) 4.47 (d, *J* 6.22 Hz, 2 H) 6.78 (m, 2 H) 6.94 (m, 1 H) 7.13 (m, 1 H) 7.22 (s, 1 H) 7.41 (s, 1 H) 7.63 (s, 1 H) 8.22 (s, 1 H)
B41-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.52 (m, 4 H) 2.83 (m, 4 H) 3.11 (s, 4 H) 4.22 (s, 3 H) 4.43 (d, *J* 6.22 Hz, 2 H) 6.88 (d, *J* 8.78 Hz, 2 H) 7.20 (d, *J* 8.66 Hz, 2 H) 7.23 (s, 1 H) 7.41 (t, 1 H) 7.57 (t, *J* 6.10 Hz, 1 H) 8.21 (s, 1 H)
B42-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (m, 2 H) 2.95 (m, 2 H) 4.27 (s, 3 H) 4.71 (d, *J* 6.22 Hz, 2 H) 6.96 (m, 1 H) 7.32 (m, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.73 (s, 1 H) 8.26 (s, 1 H).
B44-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 4 H) 4.27 (s, 3 H) 4.52 (d, *J* 5.97 Hz, 2 H) 6.24 (d, *J* 2.68 Hz, 1 H) 6.38 (dd, *J* 3.11, 1.89 Hz, 1 H) 7.23 (m, *J* 0.49 Hz, 1 H) 7.43 (s, 1 H) 7.56 (m, *J* 0.98 Hz, 2 H) 8.24 (s, 1 H)
B45-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.5-1.9 (3m, 4 H) 2.73 (m, 2 H) 2.94 (m, 2 H) 3.33 (m, 2 H) 3.6-3.8 (2m, 2 H) 4.05 (m, 1 H) 4.31 (s, 3 H) 7.10 (bs, 1 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H).
B46-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, *J*=7.62 Hz, 2 H) 2.93 (t, *J*=7.68 Hz, 2 H) 3.73 (s, 3 H) 4.19 (s, 3 H) 4.51 (d, *J*=6.34 Hz, 2 H) 6.74 - 6.82 (m, 1 H) 6.87 - 6.96 (m, 2 H) 7.16 - 7.30 (m, 2 H) 7.41 (s, 1 H) 7.68 (t, *J*=6.65 Hz, 1 H) 8.23 (s, 1 H)
B47-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (none, 2 H) 2.81 (m, 4 H) 3.10 (none, 1 H) 4.34 (s, 3 H) 7.00 (s, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.18 (s, 1 H)
B48-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (s, 6 H) 2.14 (s, 3 H) 2.22 (m, *J* 2.07 Hz, 6 H) 4.70 (s, 3 H) 7.19 (s, 1 H) 7.41 (s, 1 H) 7.48 (d, *J* 8.66 Hz, 1 H)

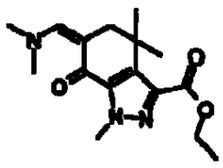
	7.76 (s, 1 H) 7.91 (d, *J* 8.66 Hz, 1 H) 9.13 (s, 1 H)
B49-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.99 (s, 3 H) 1.04 (d, *J* 7.07 Hz, 3 H) 1.19 (s, 3 H) 1.4-2.4 (5m, 8H) 2.70-3.00 (2t, 4 H) 3.34 (bs, 2 H) 4.35 (s, 3 H) 7.23-7.42 (3bs, 3 H) 8.20 (s, 1 H)
B50-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 2 H) 1.91 (d, *J* 11.71 Hz, 2 H) 2.06 (m, 2 H) 2.73 (m, *J* 7.93, 7.44 Hz, 2 H) 2.83 (d, *J* 11.34 Hz, 2 H) 2.94 (t, *J* 7.62 Hz, 2 H) 3.48 (s, 2 H) 3.70 (m, 1 H) 4.30 (s, 3 H) 7.01 (d, *J* 4.51 Hz, 1 H) 7.23 (s, 1 H) 7.30 (m, 5 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B51-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, *J*=7.62 Hz, 2 H) 2.93 (t, *J*=7.68 Hz, 2 H) 4.10 (s, 3 H) 4.60 (d, *J*=6.10 Hz, 2 H) 7.22 (s, 1 H) 7.27 (s, 2 H) 7.41 (s, 1 H) 7.51 (d, *J*=8.54 Hz, 2 H) 7.77 (d, *J*=8.41 Hz, 2 H) 7.78 - 7.83 (m, 1 H) 8.23 (s, 1 H)
B52-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 3.18 (s, 3 H) 4.63 (d, *J* 6.22 Hz, 2 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.59 (m, 2 H) 7.86 (m, 3 H) 8.24 (s, 1 H).
B53-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.11 (m, 4 H) 4.37 (s, 3 H) 4.43 (s, 3 H) 7.37 (m, 4 H) 7.57 (s, 1 H) 7.74 (m, 2 H) 8.20 (m, 2 H) 8.92 (s, 1 H).
B54-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 and2.93 (2t, 4 H, J 8.04 Hz) 4.18 (s, 3 H) 4.49 (d, 2 H, 6.34 Hz) 7.13 (m, 1 H) 7.36 (m, 1 H) 7.42 and 7.23 (2s, 2 H) 7.58 (m, 1 H) 7.73 (bs, 2 H) 8.23 (s, 1 H).
B55-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.24 (m, 2 H) 0.44 (m, 2 H) 1.13 (m, 1 H) 2.74 (m, 2 H) 2.95 (t, *J* 7.68 Hz, 2 H) 3.20 (m, 2 H) 4.32 (s, 3 H) 7.17 (t, *J* 5.79 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B56-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.80 Hz, 2 H) 3.51 - 3.75 (m, 2 H) 4.04 (dd, *J*=11.52, 6.77 Hz, 1 H) 4.27 (s, 3 H) 4.34 (dd, *J*=11.58, 2.19 Hz, 1 H) 4.38 - 4.48 (m, 1 H) 6.74 - 6.94 (m, 4 H) 7.24 (s, 1 H) 7.36 (t, *J*=5.97 Hz, 1 H) 7.44 (s, 1 H) 8.25 (s, 1 H)
B57-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.94 (m, 2 H) 4.14 (bs, 3 H) 4.62 (d, , *J* 6.22 Hz2 H) 7.23 (s, 1 H) 7.42 (s, 1 H) 7.51 (m, 2 H) 7.60 (m, 1 H) 7.83 (bs, 1 H) 9.26 (s, 1 H).
B58-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (m, 2 H) 2.95 (m, 2 H) 3.05 (m, 2 H) 3.69 (m, 2 H) 4.33 (s, 3 H) 7.24 (3m, 3 H) 7.32 (m, 1 H), 7.43 /m, 1 H) 8.22 (s, 1 H) 8.51 (m, 1 H).
B59-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 and 2.93 (2t, 4 H, J 7.56) 4.18 (s, 3 H) 6.27 (2s, 2 H) 7.22 (m,

	1 H) 7.31 (2s, 2 H) 7.37-7.43 (2m, 2 H) 7.55 (s, 1 H) 7.74 (bs, 1 H) 8.24 (s, 1 H).
B30-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.72 (s, 3 H) 6.67 (m, 1 H) 7.56 (m, 1 H) 7.44 (s, 1 H) 7.63 (s, 1 H) 8.33 (m, 1 H) 8.35 (m, 1 H) 9.73).
B45-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50-2.00 (2m, 4 H) 3.34 (m, 2 H) 3.67-3.69 (2m, 2 H) 4.18 (m, 1 H) 4.67 (s, 3 H) 7.42 (m, 1 H) 7.74 (m, 2 H) 7.88 (m, 1 H) 7.88 (m, 1 H) 9.15 (s, 1 H).
B28-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90-2.00 (6m, 11 H) 3.34 (m, 2 H) 4.67 (s, 3 H) 7.41 (bs, 1 H) 7.48 (m, 2 H) 7.86 (m, 1 H) 9.12 (s, 1 H).
B29-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.04 (m, 1 H) 4.66 (s, 3 H) 7.42 (bs, 1 H) 7.50 (m, 1 H) 7.70 (s, 1 H) 7.88 (m, 1 H) 9.15 (s, 1 H).
B50-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.65 (s, 3 H) 7.00-8.00 (m, 9H) 9.14 (s, 1 H).
B55-X00-M01(C01)-D03	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 0.31 (m, 2 H) 0.49 (m, 2 H) 1.25 (m, 1 H) 3.33 (m, 2 H) 4.68 (s, 3 H) 7.41 (s, 1 H) 7.49 (m, 2 H) 7.73 (s, 1 H) 7.75 (s, 1 H) 9.14 (s, 1 H).
B01-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (m, 4 H) 3.40 (m, 4 H) 4.31 (s, 3 H) 4.66 (s, 1 H) 6.96 (t, *J* 5.67 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.21 (s, 1 H)
B02-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 3.50 (m, 2 H) 4.32 (s, 3 H) 4.45 (m, 1 H) 7.05 (bs, 1 H) 7.23 (s, 1 H) 7.42 (s, 1 H) 8.20 (s, 1 H).
B05-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.93 (m, 2 H) 4.17 (bs, 3 H) 4.55 (d, *J* 6.22 Hz, 2 H) 7.15-7.40 (m, 7H) 7.70 (bs, 1 H) 8.23 (s, 1 H).
B69-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H) 2.74 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.68 Hz, 2 H) 3.44 (s, 3 H) 4.32 (s, 3 H) 4.46 (d, *J*=5.73 Hz, 2 H) 5.66 (dd, *J*=3.41, 0.73 Hz, 1 H) 5.84 (d, *J*=3.29 Hz, 1 H) 7.24 (s, 1 H) 7.28 (t, *J*=4.94 Hz, 1 H) 7.43 (s, 1 H) 8.24 (s, 1 H)
B70-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 and 2.95 (2t, 4 H, J 7.32 Hz) 4.24 (s, 3 H) 4.57 (d, 2 H, J 6.22 Hz) 6.13 (s, 1 H) 7.23 and 7.43 (2s, 2 H) 7.64 (bs, 1 H) 8.25 (s, 1 H)
B71-X00-M00(C01)-D03	
B72-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, *J*=7.62 Hz, 2 H) 2.94 (t, *J*=7.62 Hz, 2 H) 4.20 (s, 3 H) 4.58 (d, *J*=6.22 Hz, 2 H) 6.53 (dd, *J*=2.50, 1.77

	Hz, 1 H) 7.22 (s, 1 H) 7.41 (s, 1 H) 7.46 (d, *J*=8.66 Hz, 2 H) 7.72 (dd, *J*=1.71, 0.49 Hz, 1 H) 7.74 - 7.77 (m, 1 H) 7.77 (d, *J*=8.66 Hz, 2 H) 8.24 (s, 1 H) 8.43 (dd, *J*=2.50, 0.55 Hz, 1 H)
B74-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.96 (m, 2 H) 3.16 (s, 6 H) 4.43 (s, 3 H) 7.23 (bs, 1 H) 7.43 (bs, 1 H) 8.28 (s, 1 H).

Ejemplo 14

Etil 6-[(dimetilamino)metileno]-1,4,4-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazolo-3-carboxilato



Etapa 1 **3-metoxi-5,5-dimetil-ciclohex-2-enona**



Una solución de 5,5-dimetil-ciclohexano-1,3-diona (80,0 g, 0,57 mol) en metanol anhidro (600 mL) fueron tratados con una solución 1 M de cloruro de titanio (T_iCL_4) en diclorometano (17.2 mL). Después de agitar 1 hora a temperatura ambiente,

la mezcla fue lentamente vertida en una solución de $NaHCO_3$ fría al 5% y extraída con metil éter (450 mL x 6). Las capas orgánicas fueron recolectadas, lavadas con agua salubre, secadas sobre Na_2SO_4 y evaporadas hasta sequedad logrando el compuesto del título (81.5 g, 92% de rendimiento) como un aceite amarillo pálido.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.05 (s, 6 H) 2.19 (s, 2 H) 2.26 (s, 2 H) 3.68 (s, 3 H) 5.35 (s, 1 H).

Etapa 2. **5,5-dimetil-ciclohex-2-enona**



Una solución de 3-metoxi-5,5-dimetil-ciclohex-2-enona (80 g, 0.52 mol) el tetrahidrofurano anhidro (270 mL) fue tratado gota a gota con una solución 1 M de $LiAlH_4$ en tetrahidrofurano (182 mL), bajo atmósfera de argón y manteniendo la temperatura de la reacción entre 0°C y 5°C. A la temperatura se le permitió elevarse a 25°C y la mezcla se agitó durante 4 horas. La suspensión resultante se enfrío con un baño de hielo, se apagó con acetato de etilo (30 mL) y se vertió con precaución en una solución de H_2SO_4 enfriada 2 M. La solución acuosa fue entonces extraída con metil eter (300

mL x 3), secada sobre Na_2SO_4 y evaporada bajo presión reducida para remover la mayoría del solvente. El material crudo contenido en el compuesto del título como un aceite con bajo punto de ebullición fue utilizado en la siguiente etapa sin purificación adicional.

^{1}H NMR (300 MHz, $CHCL_3$-d) δ ppm 1.04 (s, 6 H) 2.23 (dd, *J* 4.10, 2.05 Hz, 2 H) 2.27 (s, 2 H) 6.02 (dt, *J* 9.96, 2.05 Hz, 1 H) 6.85 (dt, *J* 9.96, 4.10 Hz, 1 H).

Etapa 3 **4,4-dimetil-7-oxa-biciclo[4.1.0]reptan-2-ona**



5,5-dimetil-ciclohex-2-enona de la etapa previa (0.52 mol teórico) se disolvieron en etanol (500 mL), se enfriaron a 0°C y se trataron con 30% de peróxido de hidrógeno (265 mL, 2.6 mol). La solución resultante se trató gota a gota con solución NaOH al 2% (142 mL, 0.067 mol) manteniendo la temperatura de reacción alrededor de 0°C. La mezcla se le permitió permanecer a 4°C durante 24 horas y fue entonces diluida con agua.(900 mL) y extraída con eter de etilo (450 mL x 4).

Los extractos fueron recolectados, lavados con una solución de Na_2SO_5 al 5%, con agua salobre, secados sobre Na_2SO_4 y concentrados bajo presión reducida. El residuo fue purificado mediante destilación bajo vacío para obtener el compuesto del título (56.8 g, 78.3 de rendimiento) un aceite incoloro.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 0.91 (s, 3 H) 1.01 (s, 3 H) 1.82 (m, 2 H) 2.03 (d, *J* 15.53 Hz, 1 H) 2.64 (d, *J* 13.77 Hz, 1 H) 3.20 (dt, *J* 3.74, 0.92 Hz, 1 H) 3.49 (t, *J* 4.10 Hz, 1 H).

Etapa 4 **2-metoxi-5,5-dimetil-ciclohex-2-enona**

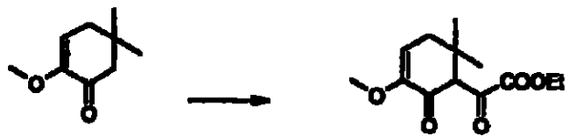


Una solución de 4,4-dimetil-7-oxa-biciclo[4.1.0]reptan-2-ona(44.0 g, 0.31 mol) en metanol (250 mL) se agregó a una solución de 85% de hidróxido de potasio (20.7 g, 0.31 mol) en metanol (450 ml) a temperatura ambiente. La mezcla se mantuvo en esta temperatura durante 20 horas y fue entonces calentada a reflujo durante 30 minutos. Después de enfriar la solución se diluyó con agua (1.2 L) y se extrajo con etil éter (350 mL x 5). Los extractos orgánicos fueron recolectados, lavados con agua salubre, secados sobre Na_2SO_4 y evaporados bajo vacío para remover la mayoría del solvente. El material crudo fue

purificado mediante destilación para obtener el compuesto del título (32.8 g, 68% de rendimiento) como un aceite.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.04 (s, 6 H) 2.30 (d, *J* 4.69 Hz, 2 H) 2.35 (s, 2 H) 3.59 (t, 3 H) 5.67 (t, *J* 4.54 Hz, 1 H).

Etapa 5 **Etil (3-metoxi-6,6-dimetil-2-oxociclohex-3-en-1-il) (oxo) acetato.**



60% de hidruro de sodio en aceite mineral (2.41 g, 60.3 mmol) fueron suspendidos entre tetrahidrofuran anhidro (60 mL) bajo atmósfera de argón y tratados con una solución de 2-metoxi-5,5-dimetil-ciclohex-2-enona (6.20 g, 40.2 mmol) en tetrahidrofurano anhidro (50 mL). Después de 15 minutos, se agregó una solución de dietil oxalato (8.17 mL, 60.3 mmol) en tetrahidrofurano anhidro (50 mL) y la mezcla se refluyó durante 1 hora. La suspensión se diluyó con agua (800 mL), se acidificó con HCL 1 N (50 mL) y se extrajo con acetato de etilo (500 mL x 2). Las capas orgánicas se reconectaron, se lavaron con agua salubre, se secaron sobre Na_2SO_4 y se evaporó hasta sequedad para obtener compuesto crudo del título (10.60

g) como un aceite de naranja, que fue utilizado sin purificación adicional.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.41 (t, 3 H) 2.77 (s, 2 H) 3.13 (s, 6 H) 4.23 (s, 3 H) 4.40 (q, *J* 7.13 Hz, 2 H) 7.58 (s, 1 H).

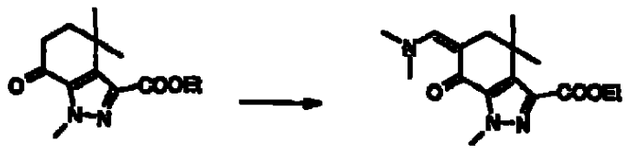
Etapa 6 Etil 1,4, 4-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato.



Una solución de etil (3-metoxi-6,6-dimetil-2-oxociclohex-3-en-1-il)(oxo)acetato de la etapa previa (40.2 mmol teórico) en ácido acético (65 mL) se trató gota a gota con una solución de metil hidracina (2.14 nL, 40.2 mmol) en ácido acético (20 mL) y se le permitió permanecer a temperatura ambiente durante toda la noche. La mezcla fue entonces diluida con agua (8900 mL) y extraída con acetato de etilo (500 mL x 2). Los extractos orgánicos fueron lavados con agua salubre, secados sobre Na_2SO_4 y evaporados hasta sequedad. El material crudo fue cromatografiado sobre sílica gel eluado con diclorometano/etil acetato 100:5 para obtener el compuesto puro del título (4.8 g, 47.7% de rendimiento).

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.42 (t, *J* 7.18 Hz, 3 H) 1.49 (s, 3 H) 1.98 (t, *J* 6.45 Hz, 2 H) 2.61 (t, *J* 6.45 Hz, 2 H) 4.19 (s, 3 H) 4.43 (q, *J* 7.03 Hz, 2 H)

Etapa 7. Etil 6-[(dimetilamino)metileno]-1,4,4-trimetil-7-oxo-4,5,67-tetrahidro-1H-indazole-3-carboxilato

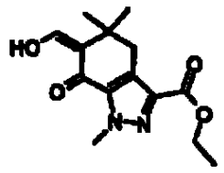


Una solución de etil 1,4,4-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato (4.8 g, 19,18 mmol) en dimetilformaida anhidra (30 mL) se extrajo con dimetilformamida di-tert-butilacetal (9.19 mL, 38.35 mmol) A 65°C durante 2 horas. La mezcla se evaporó hasta sequedad y el material crudo se cristalizó de hexano para darle compuesto del título (5.1 g, 87% de rendimiento).

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.21 (m, 9H) 2.76 (s, 2 H) 3.15 (s, 6 H) 4.22 (s, 3 H) 4.41 (q, 2 H).

Ejemplo 15

Etil 6(hidroximetileno)-1,5,5-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato



Etapa 1. **5,5-dimetil-7-oxabiciclo[4.1.0]reptan-2-ona**

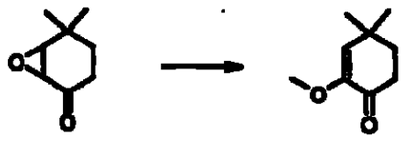


Una solución de 4, 4-dimetil-ciclohex-2-enona (32.0 g, 0.26 mol) y 30% de piróxido de hidrógeno (132 mL, 1.29 mmol) en metanol ((250 mL) se trató gota a gota con una solución de hidróxido de sodio al 2% (70 mL, 0.035 mol) manteniendo la temperatura de reacción alrededor de 0°C. a la mezcla se le permitió permanecer a 4°C durante 20 horas y luego se diluyó con agua (400 mL) y extrajo con dietileter (250 mL x 4).

Los extractos fueron recolectados, lavados con una solución de $Na_2S_2O_5$ al 5%, con agua salubre, secado sobre el Na_2SO_4, y concentrada bajo presión reducida. El residuo se purificó mediante destilación bajo vacío para obtener el compuesto del título (27.6 g, 76.4 de rendimiento) como un aceite.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.05 (s, 3 H) 1.21 (s, 3 H) 1.20-2.50 (m, 5 H) 3.20 (m, 1 H).

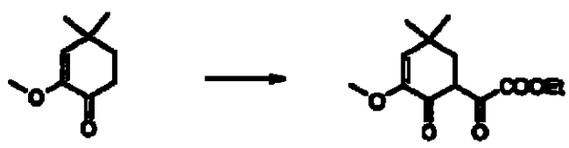
Etapa 2. 2-metoxi-4,4-dimetilciclohex-2-en-1-ona



Una solución de 5,5-dimetil-7-oxabiciclo[4.1.0]heptan-2-ona (19.4 g, 138.4 mmol) en metanol (95 mL) se agregó a una solución de 85% de hidróxido de potasio (9.1 g, 138.4 mmol) en metanol (285 mL) a temperatura ambiente. La mezcla se mantuvo a esta temperatura durante 20 horas y luego se calentó a reflujo durante 30 minutos. Después de enfriamiento, la solución se diluyó con agua (750 mL) y se extrajo con dietileter (350 mL x 4). Los extractos orgánicos fueron recolectados, lavados con agua salubre, secados sobre Na_2SO_4 y evaporados hasta sequedad. El material crudo se tomó con hexano (380 mL), se mantuvo bajo agitación vigorosa durante 30 minutos y se filtró para remover el material sólido. El filtrado se evaporó bajo vacío para obtener el compuesto puro del título (9.8 g, 45.9% de rendimiento) como un aceite amarillo pálido.

^{1}H NMR ($CDCl_3$ 400 MHz) δ ppm 1.23 (s, 6 H) 1.87 (t, 2 H) 2.61 (t, 2 H) 3.60 (s, 3 H) 5.57 (s, 1 H)

Etapa 3. Etil (3-metoxi-5,5-dimetil-2-oxociclohex-3-en-1-il) (oxo) acetato

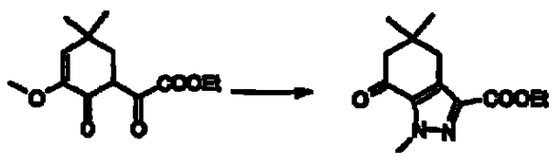


Una solución de 2-metoxi-4,4-dimetil-ciclohex-2-enona (12.5 g, 81.1 mmol) y dietil oxalato (12.1 mL, 89.2 mmol) en etil eter se trató con y una solución 1 M de litio bis(trimetilsilicio)amida en tetrahidrofurano bajo atmósfera de argón. La reacción se agitó a temperatura ambiente durante 2 horas, se virtió en una solución de NaH_2PO_4 al 10% (500 mL) y se extrajo con dietil eter (300 mL x 2). Los extractos orgánicos fueron lavados con agua salubre, secados sobre Na_2SO_4 y evaporados hasta sequedad. El material crudo fue tomado con hexano, agitado y filtrado para dar el compuesto del título (16.8 g, 81.5% de rendimiento) como un sólido cristalino amarillo.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.15 (s, 6 H) 1.38 (t, 3 H) 2.77 (s, 2 H) 3.63 (s, 3 H) 4.35 (q, 2 H) 5.62 (s, 1 H).

395

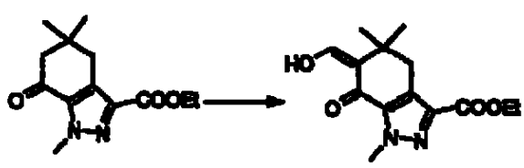
Etapa 4. Etil 1,5,5-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato



Una solución de etil (3-metoxi-5,5-dimetil-2-oxociclohex-3-en-1-il)(oxo)acetato (25.50 g, 0.061 mol) en ácido acético (100 mL) se trató gota a gota con una solución de metil hidrizina (3.49 mL, 0.066 mol) disuelta en ácido acético (50 mL). Después de 24 horas a temperatura ambiente, la mezcla de reacción se diluyó con agua (2 L) bajo agitación vigorosa. El precipitado resultante se filtró y se lavó con agua para obtener el compuesto del título (10.30 g, 67,6% de rendimiento) como un sólido amarillo.

^{1}H NMR (300 MHz, $CHCl_3$-d) δ ppm 1.20 (s, 6 H) 1.42 (t, 3 H) 2.43 (s, 2 H) 2.93 (s, 2 H) 4.21 (s, 3 H) 4.41 (q, 2 H).

Etapa 5. Etil 6-(hidroximetileno)-1,5,5-timetil-7-oxo-4,5,6,7-tetrahidro-1H-indazolo-3-carboxilato



Una solución de etil 1,5,5-trimetil-7-oxo-4,5,6,7,-tetrahidro-1H-indazolo-3-carboxilato (1.00 g, 4 mmol) en etil formato anhidro (10 mL) se trató con etóxido de sodio (0.54 g, 8 mmol) y se refluyó durante 3 horas. La mezcla se enfrío a temperatura ambiente y se vertió en agua fría (40 mL). La capa acuosa se lavó con dietileter (40 mL) para remover el material de partida que no ha reaccionado, se acidificó con una solución al 20% de NaH_2PO_4 y se extrajo con acetato de etilo (50 mL x 2). Los extractos orgánicos se recortaron, se secaron sobre Na_2SO_4 y se evaporaron hasta sequedad para obtener el compuesto del título (0.88 g, 78.8% de rendimiento) como un sólido café.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 6 H) 1.32 (t, 3 H) 2.87 (s, 2 H) 4.19 (s, 3 H) 4.30 (q, 2 H) 7.74 (s, 1 H) 14.00 (br, 1 H)

Ejemplo 16

Etil 8-amino-1-metil-1H-pirazolo[4,3-h]quinazolino-3-carboxilato

[B00-X00-M00(C01)-D01]



16.00 g (0.06 mmol) de etil-6-[(dimetilamino)metileno]-1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazolo-3-carboxilato fueron disueltos en 600 mL de etanol y 3.90 de etilato de sodio, y 5.44 de clorhidrato de guanidina se agregaron consecutivamente. La solución se agitó a reflujo durante 72 horas. El solvente fue entonces evaporado; el residuo residuelto con diclorometano y lavado con agua. La capa orgánica fue entonces secada sobre Na_2SO_4 y concentrada. El residuo se trituró con dietileter y el producto se recolectó mediante filtración (85% de rendimiento, un sólido blanco).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.28 (t, *J* 7.07 Hz, 3 H) 2.68-2.93 (m, 4 H) 4.25 (q, *J* 7.07 Hz, 2 H) 4.30 (s, 3 H) 6.54 (bs, 2 H) 8.15 (m, 1 H).

De acuerdo con esta misma metodología, pero empleando el derivado de guanidina sustituido adecuado fue preparado en los siguientes compuestos, como se reportó en la tabla VII.

Tabla VII

B04-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.82 (m, 2 H) 2.95 (m, 2 H) 4.27 (q, *J* 7.07 Hz, 2 H) 4.32 (s, 3 H) 6.93 (m, 2 H) 7.37 (m, 2 H) 7.77 (m, 2 H) 8.39 (s, 1 H) 9.49 (s, 1 H).
B06-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.84 (m, 2 H) 2.96 (m, 2 H) 4.27 (q, *J* 7.07 Hz, 2 H) 6.97 (m, 1 H) 7.30 (m, 1 H) 7.54 (m, 1 H) 7.97 (m, 1 H) 8.42 (s, 1 H) 9.74 (s, 1 H).
B07-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.85 (m, 2 H) 2.97 (m, 2 H) 4.28 (q, *J* 7.07 Hz, 2 H) 4.33 (s, 3 H) 7.28 (m, 1 H) 7.51 (m, 1 H) 7.89 (m, 2 H) 8.18 (bs, 1 H) 8.47 (s, 1 H) 9.88 (s, 1 H).
B08-X00-M00(C01)-D01	
B09-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (t, *J* 7.07 Hz, 3 H) 2.21 (s, 3 H,) 2.45 (m, 2 H) 2.81 (m, 2 H) 2.95 (m, 2 H) 3.69 (m, 4 H) 4.26 (q, *J* 7.07 Hz, 2 H) 4.33 (s, 3 H) 6.65 (m, 1 H) 7.10 (m, 1 H) 7.19 (m, 1 H) 7.21 (m, 1 H) 8.38 (s, 1 H) 9.31 (bs, 1 H).
B10-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.19 Hz, 3 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.84 (t, *J*=7.74 Hz, 2 H) 2.99 (t, *J*=7.74 Hz, 2 H) 3.10 (m, 4 H) 4.32 (q, *J*=7.19 Hz, 2 H) 4.36 (s, 3 H) 6.93 (d, *J*=9.34 Hz, 2 H) 7.53 (d, *J*=9.34 Hz, 2 H) 8.37 (s, 1 H) 9.29 (s, 1 H)
B04-X00-M00(C02)-D01	
B04-X00-M00(C04)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.82 (m, 2 H) 2.96 (m, 2 H) 3.79 (m, 2 H) 4.28 (q, *J* 7.07 Hz, 2 H) 4.78 (t, *J* 5.25 Hz, OH) 4.88

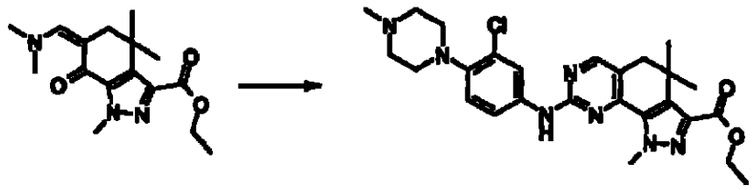
	(t, *J* 5.73 Hz, 2 H) 6.95 (m, 1 H) 7.29 (m, 2 H) 7.65 (m, 2 H) 8.39 (s, 1 H) 9.44 (bs, 1 H).
B04-X00-M00(C06)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H, J=7.07 Hz) 1.33 (t, 3 H, J=7.07 Hz) 2.90 (m, 2 H) 3.03 (m, 2 H) 4.07 (q, 2 H, J=7.07 Hz) 4.31 (q, 2 H, J=7.07 Hz) 5.73 (s, 2 H) 7.01 (m, 1 H) 7.31 (m, 2 H) 7.57 (m, 2 H) 8.44 (s, 1 H) 9.49 (bs, 1 H).
B04-X00-M00(C08)-D01	
B04-X00-M00(C09)-D01	
B04-X00-M00(C10)-D01	
B04-X00-M00(C05)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.87 (m, 2 H) 3.02 (m, 2 H) 4.36 (q, *J* 7.07 Hz, 2 H) 5.53 (q, *J* 8.90 H, 2 H) 6.90 (m, 1 H) 7.24 (m, 2 H) 7.79 (m, 2 H) 8.42 (s, 1 H) 9.74 (bs, 1 H).
B04-X00-M04(C05)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J* 7.07 Hz, 3 H) 2.87 (m, 2 H) 2.98 (m, 2 H) 4.29 (q, *J* 7.07 Hz, 2 H) 5.85 (q, *J* 8.90 Hz, 2 H) 6.80-7.60 (3m, 5 H) 8.43 (s, 1 H) 9.58 (bs, 1 H).
B04-X00-M00(C11)-D01	
B36-X00-M00(C01)-D01	
B12-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.93 (m, 8 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.36 (s, 3 H) 7.54 (d, *J* 8.90 Hz, 1 H) 7.93 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.07 (d, *J* 2.56 Hz, 1 H) 8.46 (s, 1 H) 9.78 (s, 1 H)
B13-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.28 (s, 3 H) 2.53 (m, 4 H) 2.94 (m, 8 H) 4.31 (q, *J* 7.15 Hz, 2 H) 4.38 (s, 3 H) 7.14 (d, *J* 8.90 Hz, 1 H) 7.53 (dd, *J* 8.72, 2.50 Hz, 1 H) 7.96 (d, *J* 2.44 Hz, 1 H) 8.44 (s, 1 H) 9.60 (s, 1 H)
B00-X00-M00(C00)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.2 Hz, 3 H) 2.78 (m, 2 H) 2.96 (m, 2 H) 4.31 (q, *J*=7.2 Hz, 2 H) 6.64 (m, 2 H) 8.19 (bs, 1 H)
B00-X00-M00(C03)-D01	
B00-X00-M04(C03)-D01	
B00-X00-M00(C04)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.79 - 3.88 (m, 2 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.80 (t, *J*=5.79 Hz, 1 H) 4.84 (t, *J*=5.97 Hz, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B00-X00-M00(C05)-D01	
B00-X00-M00(C08)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (t, *J*=7.07 Hz, 3 H) 2.83 (t, *J*=7.56 Hz, 2 H) 3.02 (t, *J*=7.38 Hz, 2 H) 4.36 (q, *J*=7.07 Hz, 2 H) 6.14 (s, 2 H) 7.44 (s, 2 H) 7.83 (d, *J*=8.78 Hz, 2 H) 7.92 - 7.99 (m, 2 H) 8.25 (s, 1 H)
B00-X00-M00(C09)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t,

	J=7.13 Hz, 3 H) 2.80 (t, J=7.50 Hz, 2 H) 3.00 (t, J=7.38 Hz, 2 H) 3.85 (s, 3 H) 4.34 (q, J=7.11 Hz, 2 H) 6.10 (s, 2 H) 7.03 (d, J=9.02 Hz, 2 H) 7.50 (d, J=9.02 Hz, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J=7.07 Hz, 3 H) 2.83 (t, J=7.56 Hz, 2 H) 3.01 (t, J=7.68 Hz, 2 H) 4.36 (q, J=7.15 Hz, 2 H) 6.24 (s, 2 H) 7.83 (d, J=8.78 Hz, 2 H) 7.97 (d, J=8.78 Hz, 2 H) 8.23 (s, 1 H)
B00-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, J=7.07 Hz, 3 H) 2.83 (t, J=7.50 Hz, 2 H) 3.01 (t, J=7.56 Hz, 2 H) 4.35 (q, J=7.07 Hz, 2 H) 6.02 (s, 2 H) 7.57 (ddd, J=7.53, 4.85, 1.04 Hz, 1 H) 7.68 (dt, J=7.99, 0.95 Hz, 1 H) 8.05 (td, J=7.74, 1.95 Hz, 1 H) 8.21 (s, 1 H) 8.53 (ddd, J=4.88, 1.83, 0.85 Hz, 1 H)
B00-X00-M00(C16)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, 3 H, J = 7.07 Hz) 2.82 and 3.01 (2t, 4 H, J = 7.68 Hz) 4.34 (q, 2 H, J = 7.68 Hz) 6.06 (s, 2 H) 7.46-7.60 (2m, 5 H) 8.22 (s, 1 H)
B00-X00-M00(C17)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J = 7.20 Hz) 2.76 and 2.96 (2t, 4 H, J = 7.31 Hz) 4.29 (q, 2 H, J = 7.20 Hz) 6.09 (s, 2 H) 6.64 (s, 2 H) 7.34 (m, 5 H) 8.19 (s, 1 H)
B00-X00-M00(C20)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.19 Hz) 2.09 (m, 4 H) 3.85 (m, 4 H) 4.31 (q, 2 H, J 7.19 Hz) 5.88 (m, 1 H) 6.67 (bs, 2 H) 8.08 (s, 1 H) 8.21 (s, 1 H).
B00-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 1.93 - 2.16 (m, 4 H) 2.24 - 2.43 (m, 5 H) 2.74 (t, J=7.62 Hz, 2 H) 2.88 - 3.02 (m, 4 H) 4.31 (q, J=7.07 Hz, 2 H) 5.48 - 5.69 (m, 1 H) 6.56 (s, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C21)-D01	
B00-X00-M00(C22)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 1.74 - 2.06 (m, 4 H) 2.08 (s, 3 H) 2.73 - 2.78 (m, 2 H) 2.74 - 2.86 (m, 1 H) 2.94 (t, J=7.62 Hz, 2 H) 3.28 - 3.36 (m, 1 H) 3.91 - 4.04 (m, 1 H) 4.30 (q, J=7.11 Hz, 2 H) 4.48 - 4.59 (m, 1 H) 5.78 - 5.97 (m, 1 H) 6.61 (s, 2 H) 8.20 (s, 1 H)
B00-X00-M00(C23)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.07 Hz, 3 H) 2.32 (s, 6 H) 2.76 (t, J=7.68 Hz, 2 H) 2.94 (t, J=7.50 Hz, 2 H) 3.34 (m, 2 H) 4.30 (q, J=7.07 Hz, 2 H) 4.61 (m, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B00-X00-M00(C24)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t,

	J=7.07 Hz, 3 H) 1.71 (m, 2 H) 2.32 (s, 6 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.34 (m, 2 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.61 (m, 2 H) 6.55 (s, 2 H) 8.19 (s, 1 H)
B10-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 3 H) 2.53-2.51 (m, 6 H) 2.97 and 2.51(2t, 4 H J 7.44 Hz) 3.13 (m, 4 H) 4.30 (m, 2 H) 6.96 (m, 2 H) 7.37 (m, 2 H) 8.37 (s, 1 H) 9.14 (s, 1 H).
B04-X00-M00(C21)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (t, *J*=7.07 Hz, 3 H) 1.89 - 1.96 (m, 2 H) 2.00 - 2.15 (m, 4 H) 2.79 - 2.89 (m, 4 H) 2.98 (t, *J*=7.87 Hz, 2 H) 3.52 (s, 2 H) 4.32 (q, *J*=7.15 Hz, 2 H) 5.48 - 5.66 (m, 1 H) 6.99 - 7.09 (m, 1 H) 7.21 - 7.43 (m, 7 H) 7.59 (dd, *J*=8.60, 1.04 Hz, 2 H) 8.43 (s, 1 H) 9.45 (s, 1 H)
B10-X00-M04(C15)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.26 (m, 7 H) 2.98 (m, 6 H) 3.33 (m, 2 H) 4.30 (q, 2 H) 6.32 (s, 2 H) 6.70 (d, 2 H) 7.33 (d, 2 H) 7.39 (m, 1 H) 7.47 (m, 2 H) 7.67 (m, 3 H) 8.42 (m, 1 H) 9.29 (m, 1 H)
B10-X00-M00(C15)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, 3 H) 2.30 (m, 4 H) 2.52 (m, 5 H) 2.86 (m, 2 H) 3.07 (m, 4 H) 4.33 (q, 2 H) 6.03 (s, 1 H) 6.88 (d, 2 H) 7.39 (m, 1 H) 7.51 (m, 2 H) 7.65 (m, 5 H) 8.36 (s, 1 H) 9.42 (s, 1 H)

Ejemplo 17

Etapa 8. Etil 8-{[3-cloro-4-(metilpiperazino-1-il]denil]amino}-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B13-X00-M03-(C01)-D01]



Una solución de 6-[(dimetilamino)metileno]-1,4,4-trimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazolo-3-carboxilato (0.50 g, 1.6 mmol) y N-[3-cloro-4-(4-metil-piperazin-1-il)fenil]-guanidina (1.48 g, 1.8 mmol) en dimetilformamida anhidra se calentó a 100°C y se mantuvo a esta temperatura durante 37 horas. Después de enfriamiento, la mezcla se diluyó con agua (50 mL) y el precipitado resultante se recolectó mediante filtración y se secó para dar el compuesto del título (0.72 g, 85% de rendimiento) como un sólido amarillo.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.75 (s, 2 H) 2.84 (s, 3 H) 3.33 (m, 8 H) 4.32 (q, *J* 7.07 Hz, 2 H) 4.37 (s, 3 H) 7.20 (d, *J* 8.78 Hz, 1 H) 7.57 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.01 (d, *J* 2.44 Hz, 1 H) 8.44 (s, 1 H) 9.68 (s, 1 H).

Al trabajar de acuerdo con esta metodología, y al tomar en cuenta que cuando el derivado de guanidina está disponible como una sal, Se emplearon cantidades esteichométricas de carbonato de potasio, se prepararon los siguientes compuestos:

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Etil 1,4,4-trimetil-8-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)dfenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B12-X00-M03-(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 1.34 (s, 6 H) 2.24 (s, 3 H) 2.46 (s, 4 H) 2.75 (s, 2 H) 2.84 (t, *J* 4.63 Hz, 4 H) 4.32 (q, *J* 7 11 Hz, 2 H) 4.34 (s, 3 H) 7.54 (d, *J* 8 78 Hz, 1 H) 7.93 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.06 (d, *J* 2.44 Hz, 1 H) 8.45 (s, 1 H) 9.78 (s, 1 H);

Etil 8-anilino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B04-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.74 (s, 2 H) 4.32 (q, *J* 7.15 Hz, 2 H) 4.36 (s, 3 H) 6.98 (tt, *J* 7.36, 1.07, 1.04 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.38 Hz, 2 H) 7.71 (dd, *J* 8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.54 (s, 1 H);

Etil 8-[4(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B10-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.71 (s, 2 H) 3.03 - 3.15 (m, 4 H) 4.32 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 9.28 (s, 1 H);

Etil 8-amino 1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B00-X00-M03(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.31 (s, 6 H) 2.64 (s, 2 H) 4.31 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.61 (s, 2 H) 8.18 (s, 1 H).

Ejemplo 18

Etil 8-{[3-cloro-4-(4-metilpiperazin-1-il]fenil]amino}-1,5,5-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B13-X00-M02-(C01)-D01]



Una solución de etil 6-(hidroximetileno)-1,5,5-trimetil-7-oxo-4,5,6,7,-tetrahidro-1H-indazolo-3-carboxilato (400 mg, 1.44 mmol) y N-[3-cloro-4(4-metil-piperazin-1-il)fenil]-guanidina (424 mg, 1.59 mmol) en dimetilformamida anhidra (5 mL) se calentó a 100°C durante 3 horas. Después de enfriamiento, la mezcla de reacción se vertió en agua salubre (50 mL) y se extrajo con acetato de etilo (50 mL x 2). Los extractos fueron recolectados, secados sobre Na_2SO_4 y vaporados hasta sequedad. El material crudo se purificó mediante cromatografía de destello sobre sílica gel eluada con diclorometano/metanol 9:1 para dar el compuesto del título puro (240 mg, 33% de rendimiento).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 9 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.92 (s, 2 H) 2.95 (t, *J* 4.63 Hz, 4 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.39 (s, 3 H) 7.14 (d, *J* 8.78 Hz, 1 H) 7.52 (dd, *J* 8.78, 2.44 Hz, 1 H) 7.98 (d, *J* 2.44 Hz, 1 H) 8.54 (s, 1 H) 9.63 (s, 1 H).

Al trabajar de acuerdo con esta metodología, y al tener en cuanta que cuando el derivado de guanidina está disponible como una sal, se enfriaron cantidades estechiométricas de carbonato de potasio, se prepararon los siguientes compuestos:

Etil 1,5,5,5-trimetil-8-{[4-(4-metilpiperazino-1-il)-3-(tifluorometil)fenil]amino}-4,5-dihidro-1H-pirazolo[4,6-h]quinazolina-3-carboxilato [B12-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.86 (t, *J* 4.51 Hz, 4 H) 2.93 (s, 2 H) 4.32 (q, *J* 7.15 Hz, 2 H) 4.37 (s, 3 H) 7.54 (d, *J* 8.66 Hz, 1 H) 7.93 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.09 (d, *J* 2.44 Hz, 1 H) 8.56 (s, 1 H) 9.81 (s, 1 H);

Etil 8-anilino 1,5,5-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B04-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.93 (s, 2 H) 4.31 (q, *J* 7.15 Hz, 2 H) 4.38 (s, 3 H) 6.98 (tt, *J* 7.36, 1.07, 1.04 Hz, 1 H) 7.32 (dd, *J* 8.47, 7.50 Hz, 2 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.53 (s, 1 H) 9.57 (s, 1 H);

Etil 8-amino 1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B00-X00-M03(C01)-D01]

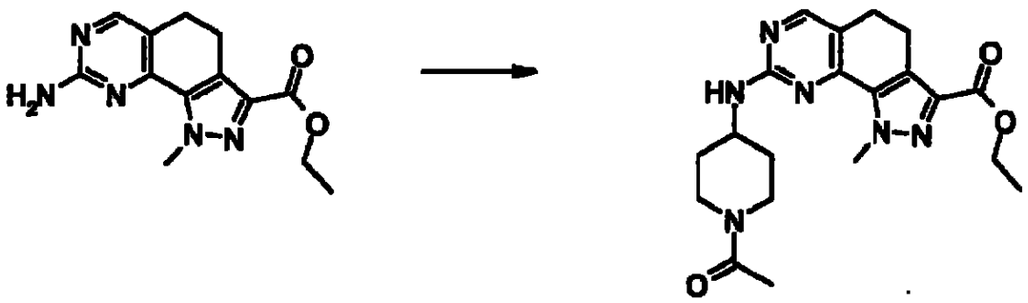
^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.30 (s, 6 H) 1.34 (t, *J*=7.07 Hz, 3 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.91 (s, 2 H) 3.09 (m, 4 H) 4.31 (q, *J*=7.19 Hz, 2 H) 4.35 (s, 3 H) 6.92 (d, *J*=9.29 Hz, 2 H) 7.52 (d, *J*=9.29 Hz, 2 H) 8.46 (s, 1 H) 9.30 (s, 1 H);

Etil 1,5,5,-trimetil-8-amino-4, 5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B00-X00-M02(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (s, 6 H) 1.32 (t, *J*=7.13 Hz, 3 H) 2.86 (s, 2 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.35 (s, 3 H) 6.61 (s, 2 H) 8.29 (s, 1 H).

Ejemplo 19

Etil 8-(1-acetil-piperidin-4-il)amino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B91-X00-M00(C01)-D01]



A una suspensión de 5.187 g (19 mmol) de etil 8-amino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato en dimetilformamida seca (120 mL), se agregó 1-acetil-4-piperidona (4.7 mL, 38 mmol), CF3COOH (10 mL, 128 mmol) y $NaBH(OAc)_3$ (8,862 g, 42 mmol). Después de 18 horas, se agregó

NaOH 0.33 N(800 mL, 264 mmol) gota a gota a la mezcla. El precipitado se filtró, se lavó con agua y se secó en un horno hasta sequedad para dar 5.3 g (70% de rendimiento) del compuesto de título.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.34 (t, *J* 7.07 Hz, 3 H) 1.47 (m, 2 H) 1.95 (m, 2 H) 2.02 (s, 3 H) 2.73 (m, 1 H) 2.77 (m, 2 H) 3.17 (m, 1 H) 3.83 (m, 1 H) 3.95 (m, 1 H) 4.30 (q, *J* 7.07 Hz, 2 H) 4.31 (m, 1 H) 4.33 (s, 3 H) 7.14 (m, 1 H) 8.24 (s, 1 H)

Al trabajar de acuerdo con el método anterior se prepararon los siguientes compuestos:

Tabla VIII

B73-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.13 Hz, 3 H) 1.54 (m, 4 H) 1.70 (m, 2 H) 1.94 (m, 2 H) 2.77 (m, 2 H) 2.94 (t, *J* 7.74 Hz, 2 H) 4.17 (m, 1 H) 4.30 (q, *J* 7.07 Hz, 2 H) 4.35 (s, 3 H) 7.11 (d, *J* 6.34 Hz, 1 H) 8.22 (s, 1 H)
B89-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.32 (t, *J* 7.13 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99 Hz, 2 H) 2.89 (m, 6 H) 3.94 (m, 3

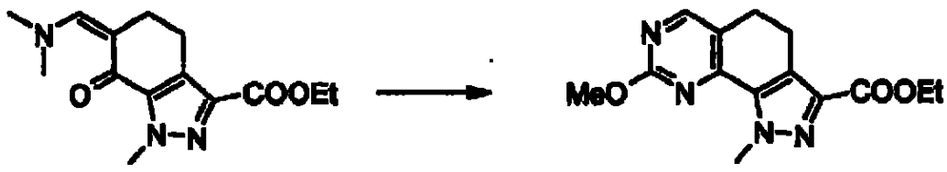
	H) 4.05 (q, *J* 7.07 Hz, 2 H) 4.30 (q, *J* 7.19 Hz, 2 H) 4.33 (s, 3 H) 7.13 (d, *J* 5.85 Hz, 1 H) 8.24 (s, 1 H)
B27-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 - 1.37 (m, 5 H) 1.32 (t, *J*=7.07 Hz, 3 H) 1.53 - 1.99 (m, 5 H) 2.76 (t, *J*=7.62 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.62 - 3.77 (m, 1 H) 4.30 (q, *J*=7.15 Hz, 2 H) 4.34 (s, 3 H) 6.98 (d, *J*=5.37 Hz, 1 H) 8.21 (s, 1 H)
B90-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.54 (m, 2 H) 1.89 (d, *J*=12.80 Hz, 2 H) 1.96 (m, 2 H) 2.18 (s, 3 H) 2.77 (m, 4 H) 2.94 (t, *J*=7.74 Hz, 2 H) 3.66 (m, 1 H) 4.30 (q, *J*=7.19 Hz, 2 H) 4.33 (s, 3 H) 7.03 (d, *J*=6.46 Hz, 1 H) 8.22 (s, 1 H)
B94-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t, J=7.2 Hz, 3 H); 1.58 (m, 2 H); 1.98 (m, 2 H); 2.75 (m, 2 H); 2.92 (m, 2 H); 3.30 (m, 2 H); 3.59 (m, 2 H); 3.72 (m, 1 H); 4.26 (s, 3 H); 4.29 (q, J=7.2 Hz, 2 H); 7.13 (d, J=7.2 Hz, 1 H); 7.68 (m, 2 H); 7.75 (m, 1 H); 7.78 (m, 2 H); 8.20 (s, 1 H)
B100-X00-M00(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.2 Hz, 3 H); 1.45 (m, 2 H); 1.90 (m, 2 H); 2.19 (m, 3 H); 2.31 (m, 4 H); 2.77(m, 2 H); 2.87(m, 2 H), 2.94 (m, 2 H); 3.15(m, 4 H); 3.60 (m, 2 H); 3.87 (m, 1 H); 4.30 (q, J=7.2 Hz, 2 H); 4.33 (s, 3 H), 7.13 (bs, 1 H); 8.23 (s, 1 H)
B73-X00-M00(C09)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 - 1.24 (m, 4 H) 1.34 (t, *J*=7.13 Hz, 3 H) 1.40 - 1.62 (m, 4 H) 2.83 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.44 Hz, 2 H) 3.83 (s, 3 H) 3.85 - 3.87 (m, 1 H) 4.34 (q, *J*=7.15 Hz, 2 H) 6.94 (s, 1 H) 7.05 (d, *J*=8.90 Hz, 2 H) 7.46 (d, *J*=9.02 Hz, 2 H) 8.18 (s, 1 H)
B73-X00-M00(C10)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.67 (m, 8 H) 1.34 (t, *J*=7.13 Hz, 3 H) 2.85 (t, *J*=7.68 Hz, 2 H) 3.03 (t, *J*=7.68 Hz, 2 H) 3.28 - 3.44 (m, 1 H) 4.35 (q, *J*=7.07 Hz, 2 H) 6.93 (s, 1 H) 7.82 (d, *J*=8.78 Hz, 2 H) 8.04 (d, *J*=8.66 Hz, 2 H) 8.22 (s, 1 H)
B73-X00-M00(C08)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.54 (m, 8 H) 1.34 (t, *J*=7.13 Hz, 3 H) 2.85 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.44 Hz, 2 H) 3.25 - 3.42 (m, 1 H) 4.30 - 4.41 (m, *J*=7.07, 7.07, 7.07 Hz, 2 H) 6.87 (s, 1 H) 7.48 (s, 2 H) 7.79 (d, *J*=8.78 Hz, 2 H) 7.95 (d, *J*=8.78 Hz, 2 H) 8.22 (s, 1 H)
B73-X00-M00(C11)-D01	
B73-X00-M00-(C19)-D01	
B91-X00-M00(C19)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J = 7.08) 2.04 (s, 3 H) 2.75 and 2.94 (2t, 4 H, J =7.32) 4.31 (q, 2 H, J = 7.08) 8.26 (s, 1 H)

B73-X00-M00 (C20)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.35 (m, 3 H) 1.50 - 1.63 (m, 4 H) 1.66 - 2.17 (m, 8 H) 2.72 - 2.86 (m, 1 H) 2.76 - 2.81 (m, 2 H) 2.94 (t, *J*=7.74 Hz, 2 H) 3.11 - 3.27 (m, 1 H) 3.86 - 3.97 (m, 1 H) 4.12 - 4.23 (m, 1 H) 4.30 (q, *J*=7.15 Hz, 2 H) 4.34 - 4.44 (m, 1 H) 5.82 - 5.98 (m, 1 H) 7.14 (s, 1 H) 8.08 (s, 1 H) 8.24 (s, 1 H)
B73-X00-M00(C22)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3H, *J*=7.07) 2.09 (s, 3H) 2.94 and 2.76 (2t, 4H, *J*=7.68) 3.18 (m, 1H) 4.02 (m, 1H) 4.18 (m, 1H) 4.30 (q, 2H, *J*=7.07 Hz) 4.56 (m, 1H) 5.88 (m, 1H) 7.13 (bs, 1H) 8.24 (s, 1H)
B91-X00-M00(C22)-D01	
B73-X00-M00(C023)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.32 (s, 6 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.34 (m, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.61 (m, 2 H) 8.20 (s, 1 H)
B73-X00-M00(C024)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.29 (s, 6 H) 2.50 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.54 (m, 2 H) 8.20 (s, 1 H)
B95-X00-M00(C01)-D01	
B91-X00-M03(C01)-D01	^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.31 (s, 6 H) 1.32 (t, *J*=7.07 Hz, 3 H) 1.49 (m, 2 H) 1.96 (m, 2 H) 2.02 (s, 3 H) 2.65 (s, 2 H) 2.76 (m, 1 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.95 (m, 1 H) 4.30 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 7.17 (s, 1 H) 8.24 (s, 1 H)
B89-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 1.35 (t, *J*=7.14 Hz, 3 H) 1.43 (m, 2 H) 1.95 (dd, *J*=12.43, 2.54 Hz, 2 H) 2.67 (s, 2 H) 2.98 (m, 2 H) 3.92 (m, 1 H) 3.99 (m, 2 H) 4.08 (q, *J*=7.00 Hz, 2 H) 4.33 (q, *J*=7.10 Hz, 2 H) 4.34 (s, 3 H) 7.17 (s, 1 H) 8.25 (s, 1
B73-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 1.32 (t, *J*=7.13 Hz, 3 H) 1.55 (m, 4 H) 1.70 (m, 2 H) 1.94 (m, 2 H) 2.64 (s, 2 H) 4.17 (m, 1 H) 4.31 (q, *J*=7.11 Hz, 2 H) 4.34 (s, 3 H) 7.12 (d, *J*=7.19 Hz, 1 H) 8.21 (s, 1 H)
B92-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.31 (s, 6 H) 1.46 (m, 2 H) 1.96 (m, 2 H) 2.65 (s, 2 H) 3.18 (m, 2 H) 3.62 (m, 1 H) 4.01 (m, 1 H) 4.31 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 4.40 (m, 1 H) 7.18 (s, 1 H) 7.34 - 7.49 (m, 5 H) 8.23 (s, 1 H)

B93-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.31 (t, *J*=7.19 Hz, 3 H) 1.59 (m, 2 H) 2.01 (m, 2 H) 2.89 (s, 3 H) 2.90 (m, 2 H) 3.56 (m, 2 H) 3.87 (m, 1 H) 4.30 (q, *J*=7.03 Hz, 2 H) 4.32 (s, 3 H) 8.24 (s, 1 H)
B94-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.31 (t, *J*=7.19 Hz, 3 H) 1.59 (m, 2 H) 1.99 (m, 2 H) 2.56 (m, 2 H) 2.63 (s, 2 H) 3.59 (m, 2 H) 3.73 (m, 1 H) 4.25 (s, 3 H) 4.30 (q, *J*=7.03 Hz, 2 H) 7.14 (d, *J*=6.83 Hz, 1 H) 7.68 (m, 2 H) 7.73 (m, 1 H) 7.77 (m, 2 H) 8.19 (s, 1 H)
B91-X00-M05	^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.37 (m, 2 H) 1.89 (m, 2 H) 2.02 (s, 3 H) 2.75 (m, 1 H) 2.93 (m, 2 H) 3.17 (m, 1 H) 3.64 (m, 2 H) 3.81 (m, 1 H) 4.01 (m, 1 H) 4.26 (m, 1 H) 4.36 (m, 2 H) 6.54 (bs, 1 H) 7.17 (s, 1 H) 8.23 (s, 1 H)

Ejemplo 20

Etil 8-metoxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B67-X03-M00(C01)-D01]



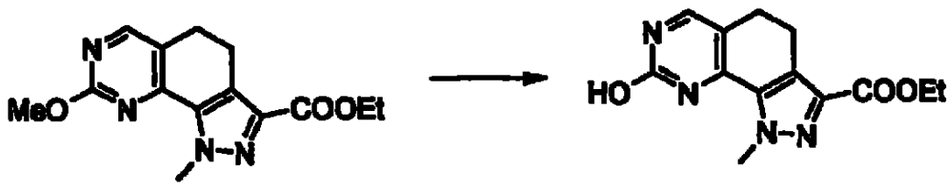
2,0 g (7.2 mmol) de etil 6-[(dimetilamino)metileno]-1-metil-7-oxo-4,5,6,7-tetrahidro-1H-indazolo-3-carboxilato se disolvieron en 200 mL de acetonitrilo y 17.4 g (70.6 mmol) de sulfato de metilisourea y se agregaron 10.0 g (72.4 mmol) de carbonato de potasio. La mezcla de reacción se agitó a

reflujo durante 16 horas. El solvente fue entonces evaporado, el residuo redisuelto en diclorometano y lavado con agua. La capa orgánica se secó sobre Na_2SO_4 anhidro y se concentró. Después de una cromatografía sobre una columna de sílica gel (eluante diclorometano) se obtuvieron 1.7 g del producto (86% rendimiento)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.07 Hz, 3 H) 2.98 (m, 4 H) 3.97 (s, 3 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.34 (s, 3 H) 8.54 (s, 1 H).

Ejemplo 21

Etil 8-hidroxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B00-X03-M00(C01)-D01]



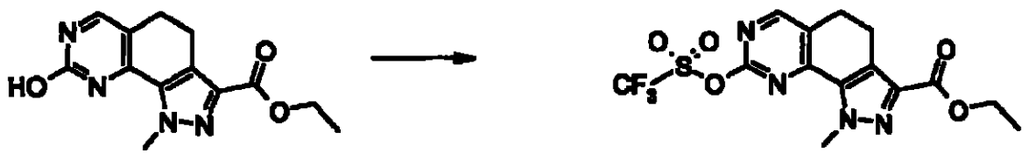
1.5 g (5.2 mmol) de etil 8-metoxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato se disolvieron en 90 mL de acetonitrilo y 1.6 g (10.6 mmol) de yoduro de sodio y se agregaron 1.5 mL de trimetilsililcloruro. Después de 1 día bajo agitación y atmósfera de nitrógeno a temperatura ambiente se evaporó el solvente, el residuo se redisolvió en una mezcla de diclorometano/metanol 4/1 y se lavó con una

solución acuosa saturada de $Na_2S_2O_3$. La capa orgánica s secó sobre Na_2SO_4 y se evaporó hasta sequedad. El residuo se cristalizó de metanol que conduce a 1.1 g del compuesto de título (78% de rendimiento).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J* 7.07 Hz, 3 H) 2.84 (m, 4 H) 4.31 (q, *J* 7.07 Hz, 2 H) 4.29 (s, 3 H) 7.87 (s, 1 H) 11.70 (s, 1 H).

Ejemplo 22

Etil 1-metil-8-{[(trifluorometil)sulfonil]oxi}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B66-X03-M00(C01)-D01]



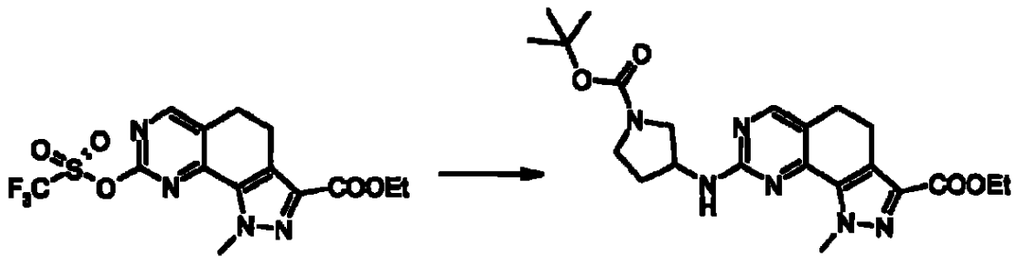
0.60 g (2.19 mmol) de etil 8-hidroxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato y se disolvió 0.31 mL (2.19 mmol) de trietilamina donde en 60 mL de diclorometano y se agitaron durante 5 horas a -78°C; luego se agregó 0.72 mL (2.19 mmol) de anhídrido tríflico. La reacción se agitó durante toda la anoche y se le permitió llegar a temperatura ambiente, se lavó con $NaHCO_3$ acuoso, se secó sobre Na_2S2O_4 y se evaporó hasta sequedad. El residuo se

trituró con dietileter/acrtina y el producto se recolectó mediante filtración dando 0.60 g (97% de rendimiento) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J* 7.13 Hz, 3 H) 3.09 (s, 4 H) 4.28 (s, 3 H) 4.32 (q, *J* 7.11 Hz, 2 H) 8.86 (s, 1 H).

Ejemplo 23

Etil 8-{[1-(tert-butoxicarbonil)pirrolidin-3-il]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato [B97-X00-M00(C01)-D01]



A una solución de 1.5 g (3.7 mmol) de etil 1-meti- 8-{[(trifluorometil)sulfonil]oxi}4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato en 150 mL de dioxano anhidro, se agregaron 756 mg (4.1 mmol) de tert-butil 3-aminopirrolidino-1-carboxilato. La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. El solvente fue entonces removido a presión reducida, el residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó

sobre sulfato de sodio y se evaporó. Se recolectó a 1.2 g (88% de rendimiento) del compuesto del título mediante filtración después de trituración con dietileter.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, *J*=7.07 Hz, 3 H) 1.38 - 1.44 (m, 9 H) 1.81 - 1.99 (m, 1 H) 2.09 - 2.23 (m, 1 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.80 Hz, 2 H) 3.13 - 3.66 (m, 4 H) 4.30 (q, *J*=7.07 Hz, 2 H) 4.32 - 4.41 (m, 1 H) 4.34 (s, 3 H) 7.40 (s, 1 H) 8.27 (s, 1 H)

Análogamente, al emplear el derivado amino adecuado, se prepararon los siguientes compuestos:

Etil 8-[(1-benzilpirrolidina-3-il)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B98-X00-MOO(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H, J 7.07 Hz) 2.21 and 1.79 (2m, 2 H) 2.51 and 2.69 (2m, 4 H) 2.93 and 2.74 (2t, 4 H, J 7.68 Hz) 4.30 (m, 5 H) 7.33 (m, 6 H) 8.23 (s, 1 H).

Ejemplo 24

8-amino-1-metil-1H-pirazolo[4,3-h]quinazolina-3-carboxamida



2,5 g de etil 8-amino-1-metil-1H-pirazolo[4,3-h]quinazolina-3-carboxilato (9.16 mmol) se disolvieron en 40 mL de metanol, 40 mL de dimetilformamida y 50 mL de una mezcla de NaH_4OH ak 30%. La mezcla se mantuvo a 65°C bajo agitación durante 1 día. El solvente fue entonces evaporado hasta sequedad, el residuo residuelto con diclorometano lavado con agua. La capa orgánica s secó sobre Na_2SO_4 y lavado con agua. La capa blanca se secó sobre Na_2SO_4 y se evaporó. El crudo se trituró con dietileter y el producto se recolectó mediante filtración (50% de rendimiento).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.68 and 2.90 (2m, 4 H) 4.28 (s, 3 H) 6.50 (bs, 2 H) 7.13-7.42 (bs, 2 H) 8.15 (s, 1 H).

Al trabajar de acuerdo con este método, se prepararon los siguientes compuestos:

Tabla IX

B04-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 2.96 (m, 2 H) 4.31 (s, 3 H) 6.94 (m, 1 H) 7.22 (bs, 1 H) 7.28 (m, 2 H) 7.68 (m, 2 H) 8.88 (s, 1 H) 9.48 (bs, 1 H).
B06-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (m, 2 H) 2.97 (m, 2 H) 4.33 (s, 3 H) 6.97 (m, 1 H) 7.29 (m, 1 H) 7.44 (bs, 1 H) 7.66 (m, 1 H) 7.98 (m, 1 H) 8.43 (s, 1 H) 9.73 (bs, 1 H).
B07-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (t, *J* 7.68 Hz, 2 H) 2.98 (t, *J* 7.74 Hz, 2 H) 4.30 (s, 3 H) 7.24 (s, 1 H) 7.26 (dd, *J* 8.66, 0.85 Hz, 1 H) 7.44 (s, 1 H) 7.51 (t, *J* 7.93 Hz, 1 H) 7.90 (d, *J* 8.05 Hz, 1 H) 8.19 (s, 1 H) 8.45 (s, 1 H) 9.87 (s, 1 H)
B08-X00-M00(C01)-D03	
B09-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (m, 2 H) 2.97 (m, 2 H) 4.31 (s, 3 H) 6.58 (m, 1 H) 7.00-7.40 (3m, 4 H) 8.37 (s, 1 H) 9.32 (bs, 1 H).
B10-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.64 (s, 3 H) 2.76 (m, 2 H) 2.95 (m, 2 H) 4.29 (s, 3 H) 6.92 (m, 2 H) 7.23 (bs, 1 H) 7.41 (bs, 1 H) 7.54 (m, 2 H) 8.32 (s, 1 H) 9.27 (bs, 1 H).
B36-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (m, 2 H) 2.95 (m, 2 H) 4.28 (s, 3 H) 5.95 (s, 2 H) 6.84 (m, 1 H) 7.06 (m, 1 H) 7.34 (m, 1 H) 7.22 (bs, 1 H) 7.42 (bs, 1 H) 8.34 (s, 1 H) 9.34 (bs, 1 H).
B04-X00-M00(C02)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.77 (s, 9H) 2.72 (m, 2 H) 2.96 (m, 2 H) 7.02 (m, 1 H) 7.20-7.40 (m, 3 H) 7.65 (m, 1 H) 7.67 (m, 1 H) 8.40 (s, 1 H) 9.21 (bs, 1 H).
B04-X00-M00(C04)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (t, *J* 7.68 Hz, 2 H) 2.96 (t, *J* 7.74 Hz, 2 H) 3.83 (q, *J* 5.69

	Hz, 2 H) 4.78 (t, *J* 5.49 Hz, 1 H) 4.84 (t, *J* 5.79 Hz, 2 H) 6.94 (t, *J* 7.38 Hz, 1 H) 7.23 (s, 1 H) 7.28 (m, 2 H) 7.43 (s, 1 H) 7.67 (d, *J* 7.68 Hz, 2 H) 8.37 (s, 1 H) 9.42 (s, 1 H)
B04-X00-M00(C07)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (m, 4 H) 5.47 (s, 2 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (t, 4 H) 7.49 (s, 1 H) 7.65 (t, *J* 7.68 Hz, 3 H) 8.41 (s, 1 H) 9.48 (s, 1 H)
B04-X00-M00(C08)-D03	
B04-X00-M00(C09)-D03	
B04-X00-M00(C10)-D03	
B04-X00-M00(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (m, 2 H) 2.92 (m, 2 H) 5.44 (q, *J* 9.02, 2 H) 6.90 (m, 1 H) 7.24 (m, 2 H) 7.80 (m, 3 H) 7.93 (bs, 1 H) 8.40 (s, 1 H) 9.72 (bs, 1 H).
B04-X00-M04(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 3.00 (m, 2 H) 5.75 (q; *J* 8.90 Hz, 2 H) 6.97 (m, 1 H) 7.28 (m, 2 H) 7.40 (bs, 1 H) 7.56 (m, 2 H) 8.42 (s, 1 H) 9.56 (bs, 1 H)
B04-X00-M00(C11)-D03	
B04-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (m, 2 H) 3.03 (m, 2 H) 6.95 (m, 1 H) 7.30 (m, 3 H) 7.51 (bs, 1 H) 7.89 (m, 2 H) 8.40 (s, 1 H) 9.45 (bs, 1 H) 14.03 (bs, 1 H).
B12-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.90 (m, 8 H) 4.33 (s, 3 H) 7.27 (s, 1 H) 7.47 (s, 1 H) 7.53 (d, *J* 8.78 Hz, 1 H) 7.93 (dd, *J* 8.90, 2.44 Hz, 1 H) 8.08 (d, *J* 2.56 Hz, 1 H) 8.45 (s, 1 H) 9.76 (s, 1 H)
B13-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.92 (m, 8 H) 4.35 (s, 3 H) 7.14 (d, *J* 8.78 Hz, 1 H) 7.27 (s, 1 H) 7.47 (s, 1 H) 7.53 (dd, *J*=8.78, 2.44 Hz, 1 H) 7.97 (d, *J*=2.56 Hz, 1 H) 8.42 (s, 1 H) 9.58 (s, 1 H)
B27-X00-M00(C03)-D03	
B27-X00-M04(C03)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (s, 3 H) 1.64 (m, 2 H) 4.85 (m, 2 H) 6.67 (m, 1 H) 7.16-7.24 (m, 3 H) 7.25-7.42 (2 bs, 2 H) 9.25 (bs, 1 H).

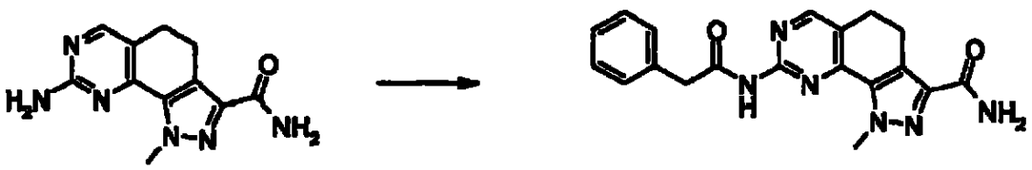
B04-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 (dd, *J*=11.58, 4.15 Hz, 2 H) 2.01 - 2.10 (m, 2 H) 2.12 - 2.23 (m, 2 H) 2.80 (t, *J*=7.56 Hz, 2 H) 2.88 (d, *J*=11.10 Hz, 2 H) 2.98 (t, *J*=7.50 Hz, 2 H) 3.52 (s, 2 H) 5.48 - 5.61 (m, 1 H) 6.99 - 7.07 (m, 1 H) 7.26 (s, 1 H) 7.27 - 7.39 (m, 7 H) 7.43 (s, 1 H) 7.60 (dd, *J*=8.54, 1.10 Hz, 2 H) 8.41 (s, 1 H) 9.43 (s, 1 H)
B00-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (d, *J*=11.95 Hz, 2 H) 2.10 - 2.33 (m, 4 H) 2.70 (t, *J*=7.74 Hz, 2 H) 2.93 (t, *J*=7.56 Hz, 4 H) 3.55 (s, 2 H) 5.41 - 5.69 (m, 1 H) 6.51 (s, 2 H) 7.15 - 7.43 (m, 7 H) 8.17 (s, 1 H)
B10-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (m, 4 H) 2.79 (m, 4 H) 3.13 (m, 4 H) 5.46 (m, 1 H) 6.95 (m, 2 H) 7.38 (m, 2 H) 7.36 and 7.26 (2s, 2 H) 8.34 (s, 1 H) 9.12 (s, 1 H).
B04-X00-M04(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (t, *J*=7.68 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 4.34 (s, 3 H) 6.92 - 7.03 (m, 1 H) 7.26 (s, 1 H) 7.31 (dd, *J*=8.41, 7.44 Hz, 2 H) 7.47 (s, 1 H) 7.72 (dd, *J*=8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B73-X00-M00(C05)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 - 1.78 (m, 6 H) 1.84 - 2.00 (m, 2 H) 2.78 (t, *J*=7.74 Hz, 2 H) 2.98 (t, *J*=7.74 Hz, 2 H) 4.02 - 4.20 (m, 1 H) 5.81 (q, *J*=8.82 Hz, 2 H) 7.22 (d, *J*=6.95 Hz, 1 H) 7.41 (s, 1 H) 7.45 (s, 1 H) 8.25 (s, 1 H)
B73-X00-M00(C04)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 - 1.77 (m, 6 H) 1.84 - 2.01 (m, 2 H) 2.73 (t, *J*=7.74 Hz, 2 H) 2.95 (t, *J*=7.56 Hz, 2 H) 3.85 (t, *J*=6.10 Hz, 2 H) 4.09 - 4.25 (m, 1 H) 4.73 - 4.90 (m, 1 H) 4.82 (t, *J*=6.16 Hz, 2 H) 7.04 (d, *J*=5.98 Hz, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B73-X00-M00(C21)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 AND 2.94 (2T, 4 H, J 7.80 Hz) 3.55 (s, 2 H) 4.15 (m, 1 H) 5.62 (m, 1 H) 7.25-7.36 (m, 5 H) 7.23 and 7.39 (2s, 2 H) 8.20 (s, 1 H).
B97-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.4 (s, 9H) 1.8-2.2 (2m, 2 H) 2.75 and 2.96 (2t, 4 H) 3.2-3.7 (m, 4 H) 4.2-4.4 (m, 4 H) 7.38 (s, 1 H) 7.24 and 7.44 (2s, 2 H) 8.25 (s, 1 H).
B98-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.6-2.2 (m, 2 H) 2.72 (m, 4 H) 2.94 (m, 4 H) 4.27 (s, 3 H) 4.32 (m, 1 H) 7.33 (m, 6 H) 7.43 (2s, 2 H) 8.21 (s, 1 H).
B95-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.19 Hz, 3 H) 1.44 - 1.58 (m, 2 H) 1.87 - 1.94 (m, 2 H) 1.95 - 2.03 (m, 2 H) 2.35 (q, *J*=7.07 Hz, 2 H) 2.73 (t, *J*=7.56 Hz, 2 H) 2.89 (d, *J*=11.71 Hz, 2 H)

	2.94 (t, J=7.62 Hz, 2 H) 3.59 - 3.78 (m, 1 H) 4.30 (s, 3 H) 7.00 (d, J=7.93 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 and 2.94 (2t, 4 H, J 7.94 Hz) 4.20 (m, 1 H) 5.60 (m, 1 H) 7.25 (s, 1 H) 1.10 and 7.35 (2s, 2 H) 8.21 (s, 1 H).
B91-X00-M00(C19)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H) 2.28 (s, 3 H) 3.18 (m, 4 H) 4.30 (m, 4 H) 5.50 (m, 1 H) 7.26 (s, 1 H) 7.10 and 7.36 (2s, 2 H) 8.24 (s, 1 H).
B91-X00-M00(C22)-D03	
B73-X00-M00(C22)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.07 (s, 3H) 2.94 and 2.72 (2t, 4H, J=7.93) 4.18 (m, 1H) 5.83 (m, 1H) 7.09 (s, 1H) 7.42 and 7.23 (2s, 2H) 8.22 (s, 1H
B73-X00-M00(C20)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.63 (m, 4 H) 1.66 - 2.15 (m, 8 H) 2.66 - 2.84 (m, 1 H) 2.72 (t, J=7.62 Hz, 2 H) 2.94 (t, J=7.68 Hz, 2 H) 3.08 - 3.39 (m, 1 H) 3.86 - 3.97 (m, 1 H) 4.10 - 4.25 (m, 1 H) 4.31 - 4.42 (m, 1 H) 5.77 - 5.95 (m, 1 H) 7.08 (s, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.09 (s, 1 H) 8.22 (s, 1 H)
B73-X00-M00(C16)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.03 - 1.64 (m, 8 H) 2.80 (t, J=7.62 Hz, 2 H) 3.03 (t, J=7.62 Hz, 2 H) 3.27 - 3.33 (m, 1 H) 6.77 (s, 1 H) 7.33 (s, 1 H) 7.44 - 7.57 (m, 5 H) 7.61 (s, 1 H) 8.17 (s, 1 H)
B73-X00-M00(C17)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.87 (m, 8 H) 2.76 (t, J=7.68 Hz, 2 H) 2.99 (t, J=7.62 Hz, 2 H) 3.99 (s, 1 H) 6.07 (s, 2 H) 7.06 (d, J=7.44 Hz, 1 H) 7.13 - 7.35 (m, 6 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C09)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00 - 1.68 (m, 8 H) 2.79 (t, J=7.62 Hz, 2 H) 3.02 (t, J=7.62 Hz, 2 H) 3.21 - 3.44 (m, 1 H) 3.82 (s, 3 H) 6.79 (d, J=5.85 Hz, 1 H) 7.04 (d, J=9.02 Hz, 2 H) 7.31 (s, 1 H) 7.46 (d, J=8.90 Hz, 2 H) 7.58 (s, 1 H) 8.16 (s, 1 H)
B73-X00-M00(C10)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 - 1.65 (m, 8 H) 2.82 (t, J=7.62 Hz, 2 H) 3.03 (t, J=7.68 Hz, 2 H) 3.25 - 3.44 (m, 1 H) 6.90 (s, 1 H) 7.42 (s, 1 H) 7.70 (s, 1 H) 7.84 (d, J=8.66 Hz, 2 H) 8.03 (d, J=8.78 Hz, 2 H) 8.21 (s, 1 H)
B73-X00-M00(C11)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.06 - 1.65 (m, 8 H) 2.82 (t, J=7.62 Hz, 2 H) 3.03 (t, J=7.68 Hz, 2 H) 3.13 - 3.62 (m, 1 H) 6.78 (s, 1 H) 7.37 (s, 1 H) 7.58 (ddd, J=7.53, 4.85, 1.04 Hz, 1 H) 7.65 (s, 1 H) 7.68 (dt, J=7.93, 0.91 Hz, 1 H) 8.04 - 8.10 (m, 1 H) 8.18 (s, 1 H) 8.57 (ddd, J=4.85, 1.86, 0.85 Hz, 1 H)

B73-X00-M00(C08)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.55 (m, 8 H) 2.82 (t, *J*=7.62 Hz, 2 H) 3.03 (t, *J*=7.56 Hz, 2 H) 3.26 - 3.42 (m, 1 H) 6.82 (s, 1 H) 7.41 (s, 1 H) 7.44 (s, 2 H) 7.64 (s, 1 H) 7.80 (d, *J*=8.66 Hz, 2 H) 7.93 (d, *J*=8.78 Hz, 2 H) 8.21 (s, 1 H)

Ejemplo 25

1-metil-8-[(fenilacetil)amino]-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B05-X01-M00(C01)D03]



0.40 G (1.47 mmol) de 8-amino-1-metil-1H-pirazolo[4,3-h]quinazolina-3-carboxamida se suspendieron en 20 mL de tetrahidrofurano y 5 mL de piridina y se agregaron 0.42 mL (3.22 mmol) de fenilacetilcloruro. La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El solvente se evaporó, el residuo se redisolvió con diclorometano, se lavó con $NaHCO_3$ acuoso y luego con agua. Después de secar sobre Na_2SO_4 anhidro el solvente se removió bajo presión reducida y el crudo se purificó mediante cromatografía sobre una columna de sílica gel (eluante ciclohexano/acetona) dando 0.35 mg del compuesto del título (60% de rendimiento).

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.62-3.02 (2m, 4 H) 3.76 (m, 2 H) 4.3 (s, 3 H) 7.00-7.50 (m, 7H) 8.50 (s, 1 H) 10.80 (bs, 1 H).

Al trabajar de acuerdo con este método, se preparó el siguiente compuesto:

8-(benzoilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B04-X01-M00(C01)D03]

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 2.87-3.04 (2m, 4 H) 4.33 (s, 3 H) 7.20-7.46 (bs, 2 H) 7.47-7.53 (m, 3 H) 7.90-8.00 (m, 2 H) 8.60 (s, 1 H) 10.97 (m, 1 H).

Ejemplo 26

Etil 8-[(aminocarbonil)amino]-1-metl-1H-pirazolo[4,3-h]quinazolina-3-carboxilato [B00-X02-M00(C01)D01]



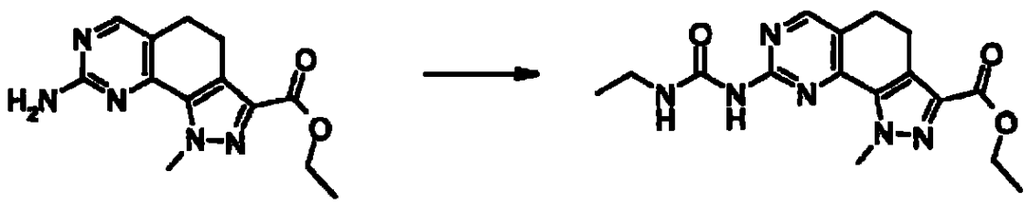
01.00 g (3.7 mmol) de etil 8-amino-1-metil-1H-pirazolo[4,3-h]quinazolina-3-carboxalato se disolvieron en 50 mL de piridina y se agregó 1 mL (8.0 mmol) de tricloroacetilisocionato. La mezcla se agito durante toda la noche a temperatura ambiente. El solvente fue entonces evaporado bajo presión reducida y el residuo se trató con 50

mL de metanol. Después de 8 horas bajo agitación el solvente se removió, el residuo se redisolvió con diclorometano y se lavó con solución diluida de hidrato de amonio. Después de secar sobre Na_2SO_4 anhidro la capa orgánica se evaporó hasta sequedad y el residuo se purificó mediante cromatografía sobre una columna de sílica gel (eluante: diclorometano/acetona) 4/1) conduciendo a 0.40 g (34% de rendimiento) del compuesto del título.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.28 (t, *J* 7.07 Hz, 3 H) 2.8-3.0 (2m, 4 H) 4.19-4.34 (1s and 1q, *J* 7.07 Hz, 3 H) 7.04 (bs, 2 H) 8.44 (bs, 1 H) 9.91 (bs, 1 H).

Ejemplo 27

Etil 8-{[(etilamino)carbonil]amino}-1-metil-1H-pirazolo[4,3-h]quinazolinO-3-carboxilato [B03-X02-M00(C01)-D01]



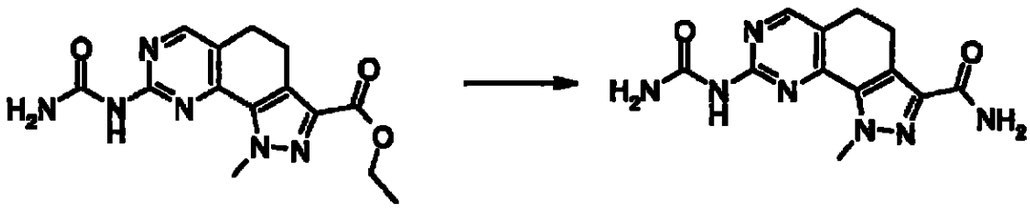
A una suspensión de 18 mg (0.44 mmol) de hidruro de sodio 60% en aceite mineral (0.37 mmol) en dimetilformamida seca, se agregó una solución de 100 mg de etil 8-amino-1-metil-1H-pirazolo[4,3-h]quinazolina-3-carboxilato (0.37 mmol) en 5mL del mismo solvente gota a gota a 0°C bajo agitación. Después de 5 minutos,, 0.070 mL (0.88 mmol) de etilsocianato se

agregaron a la mezcla y a la reacción se le permitió venir hasta temperatura ambiente. Después de 8 horas el solvente se evaporó bajo presión reducida, el residuo se redisolvió con diclorometano y se lavó con agua. Después de secar sobre Na_2SO_4 el solvente se removió y el producto purificado mediante cromatografía sobre una columna de sílica gel (eluante de clorometano/acetona) condujo a 64 mg (50% de rendimiento del compuesto del título.

^{1}H NMR (400 MHz), DMSO-d_6) δ ppm 1.10 (t, *J* 7.20 Hz, 3 H) 1.29 (t, *J* 7.07Hz, 3 H) 2.76-3.04 (2m, 4 H) 3.12 (m, 2 H) 4.21 (q, *J* 7.07 Hz, 2 H) 4.32 (s, 3 H) 8.45 (m, 1 H) 8.71 (t, 1 H) 9.70 (bs, 1 H).

Ejemplo 28

8-[(aminocarbonil)amino]-1-metil-1H-pirazolo[4,3-h]quinazolino-3-carboxamida [B00-X02-M00(C01)D03]



Una suspensión de 0.20 g (0.63 mmol) de etil 8-[(aminocarbonil)amino]1-1metil-1H-pirazolo[4,3-h]quinazolina-3-carboxilato en 15 mL de una mezcla de metanol/dimetilformamida/hidróxido de amonio 30% 1/1/1 se agitó en una botella cerrada a 65°C durante 38 horas. El

solvente fue entonces evaporado bajo presión reducida, el residuo se redisolvió con una mezcla de diclorometano/metanol 9/1 y se lavó con agua. La capa orgánica fue secada sobre Na_2SO_4 anhidro y se evaporó hasta sequedad. El producto se purificó mediante cromatografía sobre una columna de sílica gel (eluante diclorometano/acetona/metanol) dando 0.09 g (50% de renmdimiento) del compuesto del título.

^{1}H NMR (400 MHz), DMSO-d_6), δ ppm 2.91-3.09 (m, 4 H) 3.81 (s, 3 H) 6.47 (m, 3 H) 7.83 (bs, 2 H) 8.58 (m, 1 H).

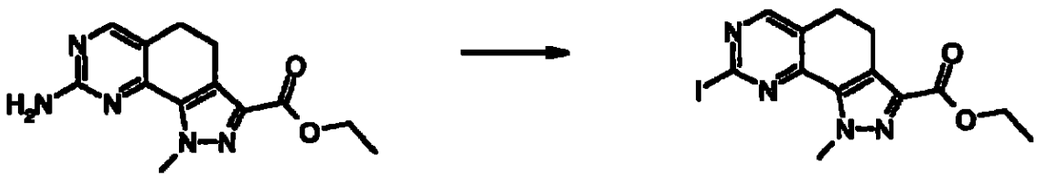
Al trabajar de acuerdo con el método anterior, se prepararon los siguientes compuestos:

8-{[(etilamino)carbonil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,4-h]quinazolina-3-carboxamida [B03-X02-M00(C01)D03]

^{1}H NMR (400 MHz), DMSO-d_6), δ ppm 1.10 (t, *J* 7.19 Hz, 3 H) 2.82 (t, *J* 7.62 Hz, 2 H) 2.97 (t, *J* 7.74 Hz, 2 H) 3.23 (m, 2 H) 4.28 (s, 3 H) 7.24 (s, 1 H) 7.45 (s, 1 H) 8.42 (s, 1 H) 8.75 (t, *J* 5.61 Hz, 1 H) 9.67 (s, 1 H).

Ejemplo 29

Etil 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolino-3-carboxilato.



A una suspensión caliente bien agitada de 8-amino-1-metil-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3-carboxamida de etilo(8.8 g, 0.032 mol) en dimetoxietano (1.2 L) mantenido en una atmósfera inerte de argon, yoduro de cesio (9.13 g, 0.035 mol), yodo bisublimado (4.45 g, 0.018 mol), yoduro de cobre(2.01 g, 0.01 mol) y nitrito isopentilo (7.00 mL, 6.14 g, 0.052 mol) fueron agregados en secuencia. La mezcla de reacción fue agitada rigurosamente entre 65-70°C durante 18 horas. Después de enfriar en un baño de agua y hielo, el sólido fue filtrado y retirado y el filtrado fue diluido con diclorometano (2.0 L), lavado con hidróxido amonico 30% (150 mL), diosulfato de sodio (300 mL), salmuera y secado sobre Na2S04 anhidro. Concentrando a un volumen cerca de 100 mL de dimetoxietano, 8-yodo-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxilato de etilo crudo se precipito; fue entonces filtrado y lavado con dimetoxietano.

La cromatografía Flash sobre gel de sílice (eluyente: diclorometano/metanol 98: 2) produjo 5.69 g del compuesto titulado. (46% de producción)

1H NMR (400 MHz), DMSO-d_6), δ ppm 1.28 (t, J 7.07 Hz, 3 H) 2. 81-3.07 (2t,J 8.90 Hz, 4 H) 4.24 (s, 3H) 4.27 (q, J7.07 Hz, 2 H) 8.5 (bs, 1H).

Trabajando de acuerdo con este método, los siguientes compuestos fueron preparados:

8-yodo-1, 4,4-trimetil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J7.1 Hz, 3 H) 1.3 (s,6 H) 2.8 (s,2 H) 4.3 (s, 3 H) 4.3 (q, J7.1 Hz, 2 H) 8.58 (s,1 H);

8-yodo-1, 5, 5-trimetil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J=7.19 Hz, 3 H) 1.32 (s, 6 H) 2.96 (s, 2 H) 4.31 (q, J=7.07 Hz, 2 H) 4.28 (s, 3 H) 8.58 (s, 1 H)

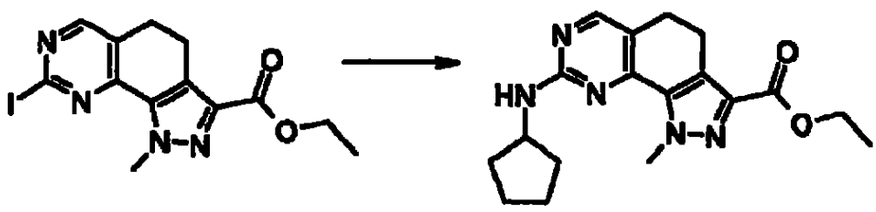
1- (3,3-dimetilbutil)-8-yodo-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxilato de etilo

2- (3,3-dimetilbutil) -8-yodo-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxilato.de etilo.

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Ejemplo 30

8-(ciclopentilamino)-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina- 3-carboxilato de etilo [B73-X00-M00 (C01)-D01]



8-iodo-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxilato de etilo(0.5 g, 1.3 mol) y ciclopentilamina (0.65 mL, 6.5 mol) fueron calentados a 100°C bajo nitrogeno durante 3 horas. La mezcla fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía sobre columna de gel de silici (eluyente: Acetato de etil /ciclohexano 70/30) para dar 0.24 g de 8-(ciclopentilamino)-1-metil-1H- pirazolo [4, 3-h] quinazolina-3-carboxilato (54% de producción).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, J 7.13 Hz, 3H) 1.54 (m, 4H) 1.70 (m, 2 H) 1.94 (m, 2H) 2.77 (m, 2H) 2.94 (t, J7.74 Hz, 2H) 4.17 (m, 1H) 4.30 (q, J7.07 Hz, 2H) 4.35 (s, 3H) 7.11 (d, J6. 34 Hz, 1H) 8.22 (s, 1H)

Trabajando de acuerdo con este método los siguientes compuestos fueron preparados:

8-{[1-(etoxicarbonil) piperidin-4-il] amino}-1-metil-4,5-dihidro-1H- pirazolo [4,3-h] quinazolina-3-carboxilato [B89-X00-M00 (C01)-D01]

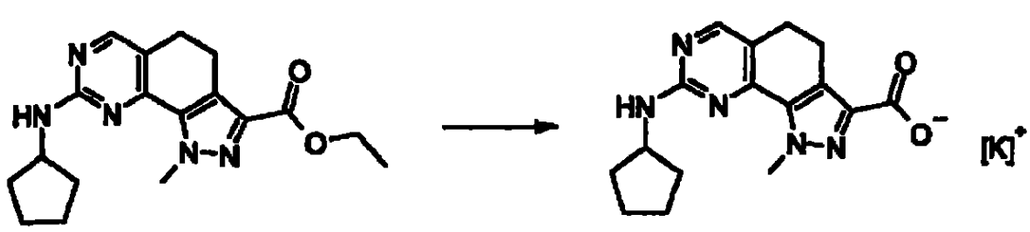
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, J7.07 Hz, 3H) 1.32 (t, J 7.13 Hz, 3H) 1.41 (m, 2H) 1.92 (dd, J 12.62, 2.99 Hz, 2H) 2.89 (m, 6H) 3.94 (m, 3H) 4.05 (q, J 7.07 Hz, 2H) 4.30 (q, J 7.19 Hz, 2H) 4.33 (s, 3H) 7.13 (d, J 5.85 Hz, 1H) 8.24 (s, 1H);

B27-X00-M00 (C03)-D01

B27-X00-M04 (C03)-D01

Ejemplo 31

8-(ciclopentilamino)-1-metil-4,5-dihidro-1H-pirazolo [4,3- h] quinazolina-3-carboxilato de potasio [B73-X00-M00 (C01)-D02]



8-(ciclopentilamino)-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxilato de etilo (230 mg, 0.67 mmol) fue suspendido en etanol anhidro (5 mL) y tratado con una solución al 1.5 M de hidroxido de potasio en etanol (1.33 mL, 3 eq.) A temperatura de reflujo durante 1.5 horas. Después de enfriar en agua con hielo el precipitado resultante fue recolectado por filtración para dar el compuesto titulado (193 mg, 82% de producción) como un sólido cristalino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (m, 6H) 1.94 (m, 2H) 2.67 (m, 2H) 2.90 (m, 2H) 4.16 (m, 1H) 4.21 (s, 3H) 6.90 (d, J6.83 Hz, 1H) 8.12 (s, 1H)

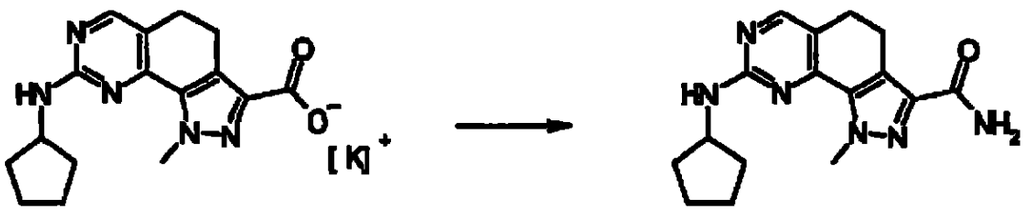
Trabajando de acuerdo con el anterior método los siguientes compuestos fueron preparados:

Tabla X

B89-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99 Hz, 2 H) 2.66 (m, 4 H) 2.91 (m, 2 H) 3.94 (m, 3 H) 4.04 (q, *J* 7.07 Hz, 2 H) 4.18 (s, 3 H) 7.13 (d, 1 H, *J* 5.85 Hz, 2 H) 8.24 (s, 1 H).
B04-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 - 2.98 (m, 1 H) 6.91 - 6.97 (m, 1 H) 7.25 - 7.30 (m, 1 H) 7.66 - 7.71 (m, 1 H)
B04-X00-M04(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, *J*=7.62 Hz, 2 H) 2.95 (t, *J*=7.68 Hz, 2 H) 4.23 (s, 3 H) 6.95 (tt, *J*=7.35, 1.13 Hz, 1 H) 7.30 (dd, *J*=8.60, 7.38 Hz, 2 H) 7.73 (dd, *J*=8.72, 1.04 Hz, 2 H) 8.32 (s, 1 H) 9.39 (s, 1 H)
B91-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (m, 2 H) 1.92 (m, 2 H) 2.02 (s, 3 H) 2.67 (m, 1 H) 2.75 (m, 1 H) 2.90 (m, 2 H) 3.16 (m, 1 H) 3.82 (m, 1 H) 3.94 (m, 1 H) 4.19 (s, 3 H) 4.28 (m, 1 H) 6.94 (m, 1 H) 8.14 (s, 1 H)
B94-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57 (m, 2 H) 1.99 (m, 2 H) 2.55 (m, 2 H) 2.63 (m, 2 H) 2.88 (m, 2 H) 3.58 (m, 2 H) 3.70 (m, 1 H) 4.11 (s, 3 H) 6.92 (d, *J*=6.95 Hz, 1 H) 7.68 (t, *J*=7.32 Hz, 2 H) 7.72 - 7.76 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.09 (s, 1 H)
B94-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.59 (m, 2 H) 1.99 (m, 2 H) 2.56 (m, 2 H) 3.58 (m, 2 H) 3.70 (m, 1 H) 4.08 (s, 3 H) 6.93 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.08 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D02	
B73-X00-M00(C04)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.99 (m, 8 H) 2.75 (t, *J*=7.68 Hz, 2 H) 2.93 (t, *J*=7.50 Hz, 2 H) 3.83 (t, 2 H) 4.10 - 4.22 (m, 1 H) 4.77 - 4.87 (m, 3 H) 7.04 (d, *J*=5.97 Hz, 1 H) 8.21 (s, 1 H) 12.61 (s, 1 H)
B90-X00-M00(C01)-D02	
B00-X00-M00(C21)-D02	
B04-X00-M00(C21)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 - 1.90 (m, 2 H) 2.00 - 2.20 (m, 4 H) 2.72 (t, *J*=7.68 Hz, 2 H) 2.88 (d,
	J=10.00 Hz, 2 H) 2.94 (t, *J*=7.50 Hz, 2 H) 3.53 (s, 2 H) 5.40 - 5.54 (m, 1 H) 6.96 - 7.04 (m, 1 H) 7.21 - 7.39 (m, 5 H) 7.26 - 7.31 (m, 2 H) 7.62 (dd, *J*=8.54, 0.98 Hz, 2 H) 8.32 (s, 1 H) 9.31 (s, 1 H)
B10-X00-M00(C19)-D02	

Ejemplo 32

8-(ciclopentilamino)-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxamida [B73-X00-M00 (C01)-D03]



Una suspensión de 8-(ciclopentilamino)-1-metil-4,5-dihidro-1H- pirazolo [4,3-h] quinazolina-3-carboxilato de potacio(180 mg, 0.51 mol) en dimetilformamida adrinosa (3.0 ml) y tetrahidrofurano adrinoso (3.0 ml) fue tratado con N-etil-N, N-diisopropilamina (0.175 mL, 2 eq.) y hidrocloruro N-etil-N', N'-diisopropil carbodiimida (EDCI) (195 mg, 2 eq). La mezcla fue entonces enfriada a 0°C y tratada con amonio 1H-1, 2, 3-benzotriazol-1-ate (137 mg, 2 eq). Después de 5 minutos la reacción fue calentada a temperatura ambiente y mantenida a esta temperatura durante la noche. La reacción fue diluida con agua y el precipitado resultante fue recolectado por filtración para proporcionar el compuesto titulado (143 mg, 90 % de producción).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6H) 1.94 (m, 2H) 2.73 (m, 2H) 2.95 (t, J7. 62 Hz, 2H) 4.17 (m, 1H) 4.32 (s, 3H) 7.08 (d, J6. 83 Hz, 1H) 7.23 (s, 1H) 7.43 (s,1H) 8.20 (s, 1H)

Trabajando de acuerdo con el anterior método los siguientes compuestos fueron preparados:

Tabla XI:

B89-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J* 7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J* 12.62, 2.99, 2 H) 2.74 (m, 2 H) 2.91 (m, 2 H) 2.95 (m, 4 H) 3.94 (m, 3 H) 4.04 (q, *J* 7.07 Hz, 2 H) 4.30 (s, 3 H) 7.09 (bs, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.22 (s, 1 H).
B91-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (m, 2 H) 1.92 (m, 2 H) 2.02 (s, 3 H), 2.74 (m, 2 H) 2.76 (m, 1 H) 2.95 (m, 2 H) 3.16 (m, 1 H) 3.81 (m, 1 H) 3.94 (m, 1 H) 4.27 (m, 1 H) 4.31 (s, 3 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.23 (s, 1 H)

B100-X00-M00(C01)-D03 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 - 1.57 (m, 2 H) 1.95 (d, *J*=12.19 Hz, 2 H) 2.74 - 2.83 (m, 5 H) 2.89 - 3.53 (m, 10 H) 3.65 (dd, *J*=12.50, 7.87 Hz, 4 H) 3.96 (t, *J*=10.61 Hz, 1 H) 4.30 (s, 3 H) 7.29 (s, 1 H) 7.47 (s, 1 H) 7.64 (s, 1 H) 8.26 (s, 1 H) 10.39 (s, 1 H)
B93-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSOd_6) δ ppm 1.60 (m, 2 H) 2.01 (m, 2 H) 2.74 (m, 2 H) 2.89 (m, 7H,) 3.55 (m, 2 H.) 3.86 (m, 1 H) 4.31 (s, 3 H) 7.15 (bd, 1 H) 7.24 (s, 1 H) 7.44 (s, 1 H) 8.24 (s, 1 H)
B92-X00-M00(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (s, 2 H) 1.99 (s, 2 H) 2.78 (t, *J*=7.56 Hz, 2 H) 2.98 (t, *J*=7.62 Hz, 2 H) 3.01 - 3.76 (m, 3 H) 4.05 (m, 1 H) 4.30 (s, 3 H) 4.41 (m, 1 H) 7.27 (s, 1 H) 7.40 (m, 2 H) 7.47 (m, 4 H) 7.60 (s, 1 H) 8.25 (s, 1 H)
B95-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.19 Hz, 3 H) 1.52 (m, 2 H) 1.90 (m, 2 H) 1.98 (m, 2 H) 2.35 (q, *J*=7.07 Hz, 2 H) 2.73 (t, *J*=7.56 Hz, 2 H) 2.89 (d, *J*=11.71 Hz, 2 H) 2.94 (t, *J*=7.62 Hz, 2 H) 3.66 (m, 1 H) 4.30 (s, 3 H) 7.00 (d, *J*=7.93 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.21 (s, 1 H)
B73-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B91-X00-M00(C00)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (m,1 H); 1.46 (m, 1 H); 1.90 (m, 1 H);1.96 (m, 1 H); 2.02 (s,3 H); 2.74 (d, J=5 Hz, 3 H); 2.74 (m, 2 H); 2.75 (m, 1 H); 2.95 (m, 2 H); 3.16 (m, 1 H); 3.82 (m, 1 H); 3.95 (m,1 H); 4.29 (m, 1 H); 4.31 (s, 3 H); 7.11(bs, 1 H); 8.05 (q, J=4.5 Hz, 1 H); 8.23(s, 1 H)
B94-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.53 - 1.68 (m, 2 H) 1.92 - 2.05 (m, 2 H) 2.52 - 2.62 (m, 2 H) 2.71 (t, *J*=7.62 Hz, 2 H) 2.89 - 2.98 (m, 2 H) 3.53 - 3.63 (m, 2 H) 3.65 - 3.79 (m, 1 H) 4.24 (s, 3 H) 7.10 (d, *J*=7.32 Hz, 1 H) 7.23 (s, 1 H) 7.41 (s, 1 H) 7.65 - 7.70 (m, 2 H) 7.72 - 7.78 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.19 (s, 1 H)
B73-X00-M00(C023)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.32 (s, 6 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 3.34 (m, 2 H) 4.17 (m, 1 H) 4.61 (m, 2 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B73-X00-M00(C024)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 (m, 6 H) 1.94 (m, 2 H) 2.29 (s, 6 H) 2.50 (m, 2 H) 2.73 (m, 2 H) 2.95 (t, *J* 7.62 Hz, 2 H) 4.17 (m, 1 H) 4.54 (m, 2 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.43 (s, 1 H) 8.20 (s, 1 H)
B79-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65 - 1.82 (m, 2

	H) 2.05 - 2.16 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.75 - 2.80 (m, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 3.01 - 3.09 (m, 2 H) 3.27 - 3.49 (m, 2 H) 3.93 - 4.10 (m, 1 H) 4.31 (s, 3 H) 7.59 (s, 1 H) 8.07 (q, *J*=4.47 Hz, 1 H) 8.26 (s, 1 H) 8.44 - 8.63 (m, 1 H) 8.69 - 8.90 (m, 1 H)
B90-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 - 1.62 (m, 2 H) 1.90 (d, *J*=13.05 Hz, 2 H) 2.00 - 2.08 (m, 2 H) 2.21 (s, 3 H) 2.70 - 2.76 (m, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 2.78 - 2.84 (m, 2 H) 2.95 (t, *J*=7.56 Hz, 2 H) 3.62 - 3.75 (m, 1 H) 4.31 (s, 3 H) 7.01 (d, *J*=7.68 Hz, 1 H) 8.06 (q, *J*=4.59 Hz, 1 H) 8.21 (s, 1 H)
B90-X00-M00(C01)-D27	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.68-2.82 (m, 4 H) 2.73 and 2.95 (2t, 4 H J 7.44 Hz) 3.67 (m, 1 H) 4.30 (s, 3 H) 7.01 (bs, 1 H) 8.11 (d, 1 H, J 4.51 Hz) 8.21 (s, 1 H)
B89-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.07 Hz, 3 H) 1.41 (m, 2 H) 1.92 (dd, *J*=12.68, 2.68 Hz, 2 H) 2.70 - 2.79 (m, 5 H) 2.95 (t, *J*=7.68 Hz, 4 H) 3.84 - 3.99 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.30 (s, 3 H) 7.09 (d, *J*=5.98 Hz, 1 H) 8.06 (q, *J*=4.39 Hz, 1 H) 8.22 (s, 1 H)
B91-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (m, 2 H) 1.94 (m, 2 H) 2.02 (s, 3 H), 2.74 (m, 5 H) 2.96 (m, 2 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.94 (m, 1 H) 4.27 (m, 1 H) 4.31 (s, 3 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.23 (s, 1 H) 7.44 (s, 1 H) 8.23 (s, 1 H)
B73-X00-M00(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.73 (m, 2 H) 1.97 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.79 (t, *J*=7.62 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 4.21 (s, 1 H) 4.32 (s, 3 H) 7.68 - 7.92 (m, 1 H) 8.12 (q, *J*=4.39 Hz, 1 H) 8.24 (s, 1 H)
B100-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.43 - 1.51 (m, 2 H) 1.91 (dd, *J*=12.68, 3.17 Hz, 2 H) 2.21 (s, 3 H) 2.33 (s, 4 H) 2.71 - 2.76 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.82 - 2.91 (m, 2 H) 2.95 (t, *J*=7.62 Hz, 2 H) 3.12 - 3.18 (m, 4 H) 3.60 (dt, *J*=13.32, 3.34 Hz, 2 H) 3.80 - 3.95 (m, 1 H) 4.30 (s, 3 H) 7.09 (s, 1 H) 8.06 (q, *J*=4.63 Hz, 1 H) 8.22 (s, 1 H)
B92-X00-M00(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 (s, 2 H) 1.99 (s, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.78 (m, 2 H) 2.98 (t, *J*=7.68 Hz, 2 H) 3.06 - 3.79 (m, 3 H) 4.05 (m, 1 H) 4.30 (s, 3 H) 4.41 (m, 1 H) 7.37 - 7.43 (m, 2 H) 7.45 - 7.49 (m, 3 H) 7.60 (s, 1 H) 8.10 (q, *J*=4.63 Hz, 1 H) 8.25 (s, 1 H)
B93-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSOd$_6$) δ ppm 1.60 (m, 2 H) 2.01 (m, 2 H) 2.74 (m, 5 H) 2.89 (m, 3 H,) 2.95 (m, 4 H) 3.56 (m, 2 H.) 3.86 (m, 1 H) 4.31 (s, 3 H) 7.15 (bd, 1 H) 8.05 (m, 1 H) 8.24 (s, 1 H)

B96-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 - 1.46 (m, 2 H) 1.42 (s, 9 H) 1.84 - 1.94 (m, 2 H) 2.71 - 2.77 (m, 2 H) 2.75 (d, *J*=4.76 Hz, 3 H) 2.93 (m, 4 H) 3.94(m, 3 H) 4.30 (s, 3 H) 7.09 (d, *J*=4.15 Hz, 1 H) 8.07 (m, 1 H) 8.22 (s, 1 H)
B94-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 (m, 2 H) 1.98 (m, 2 H) 2.53 - 2.61 (m, 2 H) 2.67 - 2.77 (m, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 2.93 (m, 2 H) 3.58 (d, *J*=13.90 Hz, 2 H) 3.72 (m, 1 H) 4.24 (s, 3 H) 7.10 (d, *J*=7.07 Hz, 1 H) 7.64 - 7.71 (m, 2 H) 7.72 - 7.77 (m, 1 H) 7.76 - 7.80 (m, 2 H) 8.04 (q, *J*=4.59 Hz, 1 H) 8.19 (s, 1 H)
B73-X00-M00(C01)-D26 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.72 (m, 2 H) 1.97 (m, 2 H) 2.79 (m, 2 H) 2.86 (m, 11 H) 3.01 (m, 2 H) 3.81 (s, 1 H) 4.03 (s, 1 H) 4.21 (m, 1 H) 4.33 (m, 3 H) 7.70 (m, 1 H) 8.25 (s, 1 H)
B73-X00-M00(C01)-D10 dihydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.58 (m, 4 H) 1.72 (m, 2 H) 1.96 (m, 2 H) 2.79 (m, 2 H) 2.82 (d, *J*=2.2 Hz, 3 H) 2.87 (m, 2 H) 3.0-3.7 (m, 6 H) 4.21 (m, 1 H) 4.32 (s, 3 H) 4.60 (m, 1 H) 4.80 (m, 1 H) 7.70 (m, 1 H) 8.26 (s, 1 H)
B73-X00-M00(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.94 (m, 2 H) 2.76 (m, 2 H) 2.94 (m, 2 H) 4.17 (m, 1 H) 4.22 (d, *J*=5.68 Hz, 2 H) 4.36 (s, 3 H) 7.10 (bd, 1 H) 8.22 (s, 1 H) 8.35 (t, *J*=5.68 Hz, 1 H)
B73-X00-M00(C01)-D30	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.93 (m, 2 H) 2.74 (m, 2 H) 2.96 (m, 2 H) 3.81 (d, *J*=5.68 Hz, 2 H) 4.17 (m, 1 H) 4.35 (s, 3 H) 7.07 (m, 2 H) 7.38 (bs, 1 H) 8.015 (t, *J*=5.68 Hz, 1 H)8.21 (s, 1 H)
B73-X00-M00(C01)-D05	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46 - 1.61 (m, 4 H) 1.64 - 1.78 (m, 2 H) 1.87 - 2.01 (m, 2 H) 2.67 - 2.89 (m, 4 H) 3.35 (s, 3 H) 4.11 - 4.23 (m, 1 H) 4.31 (s, 3 H) 7.06 (d, *J*=6.58 Hz, 1 H) 8.20 (s, 1 H) 9.88 (s, 1 H)
B73-X00-M00(C01)-D72	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (m, 4 H) 1.71 (m, 2 H) 1.92 (m, 2 H) 2.23 (s, 6 H) 2.52 (m, 2 H) 2.71 (m, 2 H) 2.91 (m, 4 H) 4.17 (m, 1 H) 4.37 (s, 3 H) 5.09 (m, 1 H) 7.07 (d, *J* 6.83 Hz, 1 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.20 (s, 1 H) 8.28 (m, 1 H)
B73-X00-M00(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (m, 3 H) 1.65 (m, 6 H) 1.94 (m, 2 H) 2.17 (s, 6 H) 2.45 (m, 2 H) 2.73 (m, 2 H) 2.95 (m, 2 H) 4.04 (m, 1 H) 4.17 (m, 1 H) 4.32 (s, 3 H) 7.08 (d, *J* 6.83 Hz, 1 H) 7.91 (d, 1 H) 8.20 (s, 1 H)
B94-X00-M00(C01)-D72	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61 (m, 2 H) 1.97 (m, 2 H) 2.23 (s, 6 H) 2.52 (m, 2 H) 2.55 (m, 2 H) 2.70 (m, 2 H) 2.90 (m, 4 H) 3.56 (m, 2 H) 3.72 (m, 1 H) 4.28 (s, 3 H) 5.10 (m, 1 H) 7.11 (d, *J* 6.83 Hz, 1 H) 7.24

	(m, 1 H) 7.33 (m, 2 H) 7.40 (m, 2 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.18 (s, 1 H) 8.27 (m, 1 H)
B94-X00-M00(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (m, 3 H) 1.61 (m, 2 H) 2.00 (m, 2 H) 2.19 (s, 6 H) 2.52 (m, 2 H) 2.55 (m, 2 H) 2.72 (m, 2 H) 2.94 (m, 2 H) 3.57 (m, 2 H) 3.73 (m, 1 H) 4.10 (m, 1 H) 4.25 (s, 3 H) 7.09 (m, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.19 (s, 1 H)
B91-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.43 (m, 2 H) 1.94 (m, 2 H) 2.02 (s, 3 H) 2.62 (s, 2 H) 2.76 (m, 1 H) 3.16 (m, 1 H) 3.83 (m, 1 H) 3.94 (m, 1 H) 4.28 (m, 1 H) 4.29 (s, 3 H) 7.12 (d, *J*=4.15 Hz, 1 H) 7.27 (s, 1 H) 7.53 (s, 1 H) 8.21 (s, 1 H)
B89-X00-M03(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.07 Hz, 3 H) 1.34 (s, 6 H) 1.38 - 1.49 (m, 2 H) 1.89 - 1.99 (m, 2 H) 2.65 (s, 2 H) 2.90 - 3.04 (m, 2 H) 3.90 - 4.00 (m, 3 H) 4.06 (q, *J*=7.07 Hz, 2 H) 4.29 (s, 3 H) 7.31 (s, 1 H) 7.57 (s, 1 H) 8.24 (s, 1 H) 8.41 (s, 2 H)
B73-X00-M03(C01)-D03 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 1.51 - 1.77 (m, 6 H) 1.85 - 2.04 (m, 2 H) 2.67 (s, 2 H) 4.14 - 4.25 (m, 1 H) 4.31 (s, 3 H) 7.34 (s, 1 H) 7.60 (s, 1 H) 7.86 (s, 1 H) 8.23 (s, 1 H)
B92-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.50 (m, 2 H) 1.99 (m, 2 H) 2.62 (s, 2 H) 3.10 (m, 2 H) 3.62 (m, 1 H) 4.01 (m, 1 H) 4.29 (s, 3 H) 4.40 (m, 1 H) 7.15 (s, 1 H) 7.27 (s, 1 H) 7.38 (m, 2 H) 7.47 (m, 3 H) 7.53 (s, 1 H) 8.22 (s, 1 H)
B94-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.60 (m, 2 H) 1.99 (m, 2 H) 2.52 (s, 2 H) 2.59 (m, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.57 (m, 2 H) 3.71 (m, 1 H) 4.22 (s, 3 H) 7.11 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.11 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.60 (m, 2 H) 2.02 (m, 2 H) 2.62 (s, 2 H) 2.89 (m, 5 H) 3.55 (m, 2 H) 3.85 (m, 1 H) 4.30 (s, 3 H) 7.15 (bd, 1 H) 7.27 (s, 1 H) 7.53 (s, 1 H) 8.22 (s, 1 H)
B91-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.34 - 1.52 (m, 2 H) 1.87 - 2.00 (m, 2 H) 2.02 (s, 3 H) 2.62 (s, 2 H) 2.71 - 2.84 (m, 1 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.10 - 3.22 (m, 1 H) 3.83 (d, *J*=12.93 Hz, 1 H) 3.89 - 4.02 (m, 1 H) 4.23 - 4.35 (m, 1 H) 4.30 (s, 3 H) 7.13 (d, *J*=4.88 Hz, 1 H) 8.13 (q, *J*=4.72 Hz, 1 H) 8.22 (s, 1 H)
B73-X00-M03(C01)-D04 hydrochloride	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 1.50 - 1.65 (m, 4 H) 1.67 - 1.78 (m, 2 H) 1.88 - 2.08 (m, 2 H) 2.67 (s, 2 H) 2.76 (d, *J*=4.63 Hz, 3 H) 4.09 - 4.24 (m, 1 H) 4.31 (s, 3 H) 7.84 (s, 1 H) 8.20 (q, *J*=4.51 Hz, 1 H) 8.23 (s, 1 H)
B92-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H)

	1.50 (m, 2 H) 1.99 (m, 2 H) 2.62 (s, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.14 (m, 2 H) 3.63 (m, 1 H) 4.01 (m, 1 H) 4.29 (s, 3 H) 4.43 (m, 1 H) 7.15 (s, 1 H) 7.39 (m, 2 H) 7.47 (m, 3 H) 8.13 (m, 1 H) 8.22 (s, 1 H)
B94-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (s, 6 H) 1.60 (m, 2 H) 1.99 (m, 2 H) 2.52 (s, 2 H) 2.59 (m, 2 H) 2.75 (d, *J*=4.51 Hz, 3 H) 3.57 (m, 2 H) 3.71 (m, 1 H) 4.22 (s, 3 H) 7.11 (s, 1 H) 7.68 (m, 2 H) 7.77 (m, 3 H) 8.11 (m, 1 H) 8.18 (s, 1 H)
B93-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 1.60 (m, 2 H) 2.02 (m, 2 H) 2.62 (s, 2 H) 2.75 (d, 3 H) 2.89 (m, 5 H) 3.55 (m, 2 H) 3.85 (m, 1 H) 4.30 (s, 3 H) 7.16 (bd, 1 H) 8.13 (d, 1 H) 8.22 (s, 1 H)
B89-X00-M03(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.13 Hz, 3 H) 1.33 (s, 6 H) 1.35 - 1.50 (m, 2 H) 1.93 (m, 2 H) 2.64 (s, 2 H) 2.86 - 3.06 (m, 2 H) 3.84 - 4.00 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.25 (d, *J*=5.73 Hz, 2 H) 4.33 (s, 3 H) 7.14 (s, 1 H) 8.23 (s, 1 H) 8.92 (t, *J*=5.79 Hz, 1 H)
B89-X00-M03(C01)-D138	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.13 Hz, 3 H) 1.22 (s, 6 H) 1.42 (m, 2 H) 1.94 (m, 2 H) 2.62 (s, 2 H) 3.0 (m, 5 H) 3.54 (m, 2 H) 3.63 (m, 2 H) 3.95 (m, 3 H) 4.05 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 7.14 (s, 1 H) 8.23 (s, 1 H) 8.92 (t, *J*=5.79 Hz, 1 H)

En la tabla XII ver el HPLC/deto de masa para algunos compuestos representativos de la invención

Tabla XII

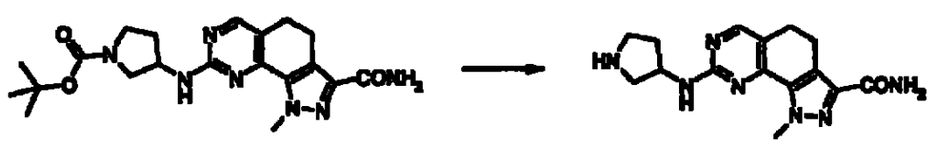
	M+H	Time	Method
B89-X00-M03(C01)-D05	444.23	2.07	2
B89-X00-M03(C01)-D31	500.29	2.6	2
B89-X00-M03(C01)-D32	500.29	2.44	2
B89-X00-M03(C01)-D33	498.24	2.85	2
B89-X00-M03(C01)-D136	541.32	1.73	2
B89-X00-M03(C01)-D137	515.3	1.79	2
B89-X00-M03(C01)-D17	555.33	1.88	2
B89-X00-M03(C01)-D76	541.32	2	2
B89-X00-M03(C01)-D78	486.28	2.29	2
B89-X00-M03(C01)-D79	516.29	1.91	2
B89-X00-M03(C01)-D14	496.3	3.16	2
B89-X00-M03(C01)-D80	486.28	2.21	2
B89-X00-M03(C01)-D44	519.28	2.49	2
B89-X00-M03(C01)-D81	539.34	1.98	2

B89-X00-M03(C01)-D12	486.28	2.55	2
B89-X00-M03(C01)-D25	467.24	2.66	2
B89-X00-M03(C01)-D82	486.28	2.27	2
B89-X00-M03(C01)-D83	530.26	2.41	2
B89-X00-M03(C01)-D84	519.28	2.66	2
B89-X00-M03(C01)-D85	487.27	2.18	2
B89-X00-M03(C01)-D60	548.29	2.83	2
B89-X00-M03(C01)-D86	499.31	1.8	2
B89-X00-M03(C01)-D87	548.29	2.94	2
B89-X00-M03(C01)-D88	510.31	3.37	2
B89-X00-M03(C01)-D89	481.26	2.51	2
B89-X00-M03(C01)-D90	504.24	3.03	2
B89-X00-M03(C01)-D91	514.27	2.82	2
B89-X00-M03(C01)-D92	498.28	2.25	2
B89-X00-M03(C01)-D93	540.32	2.49	2
B89-X00-M03(C01)-D94	474.26	2.65	2
B89-X00-M03(C01)-D04	442.25	2.48	2
B89-X00-M03(C01)-D95	502.27	2	2
B89-X00-M03(C01)-D34	548.29	2.8	2
B89-X00-M03(C01)-D96	510.24	3.09	2
B89-X00-M03(C01)-D97	486.28	2.27	2
B89-X00-M03(C01)-D45	519.28	2.52	2
B89-X00-M03(C01)-D98	500.29	2.43	2
B89-X00-M03(C01)-D99	528.29	2.86	2
B89-X00-M03(C01)-D100	526.31	2.22	2
B89-X00-M03(C01)-D06	472.26	2.15	2
B89-X00-M03(C01)-D101	514.31	2.62	2
B89-X00-M03(C01)-D102	456.26	2.67	2
B89-X00-M03(C01)-D103	512.29	2.03	2
B89-X00-M03(C01)-D104	486.28	2.27	2
B89-X00-M03(C01)-D105	512.2	2.15	2
B89-X00-M03(C01)-D106	498.31	3.22	2
B89-X00-M03(C01)-D107	512.25	2.52	2
B89-X00-M03(C01)-D108	615.33	2.98	2
B89-X00-M03(C01)-D109	561.32	3.4	2
B89-X00-M03(C01)-D110	515.27	1.99	2
B89-X00-M03(C01)-D111	528.32	2.76	2
B89-X00-M03(C01)-D112	533.29	2.76	2
B89-X00-M03(C01)-D113	512.29	2.27	2
B89-X00-M03(C01)-D114	583.33	2.9	2
B89-X00-M03(C01)-D115	525.32	1.91	2

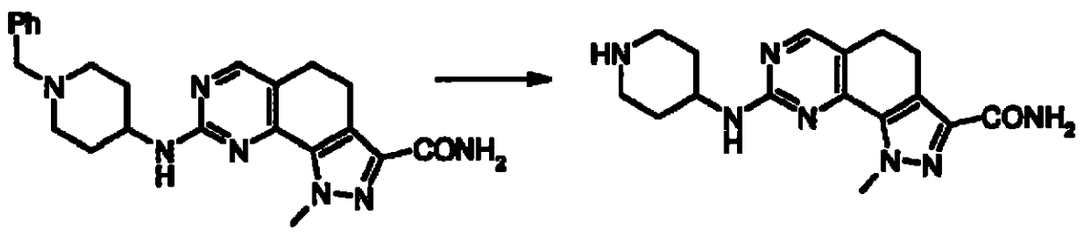
B89-X00-M03(C01)-D116	539.34	1.95	2
B89-X00-M03(C01)-D117	514.31	2.64	2
B89-X00-M03(C01)-D118	500.29	2.52	2
B89-X00-M03(C01)-D119	502.27	2.02	2
B89-X00-M03(C01)-D120	482.28	3.06	2
B89-X00-M03(C01)-D121	553.32	2.32	2
B89-X00-M03(C01)-D122	526.31	2.38	2
B89-X00-M03(C01)-D123	498.28	2	2
B89-X00-M03(C01)-D124	456.26	2.25	2
B89-X00-M03(C01)-D125	602.26	3.64	2
B89-X00-M03(C01)-D126	584.3	3.2	2
B89-X00-M03(C01)-D127	603.33	3.08	2
B89-X00-M03(C01)-D128	565.35	1.99	2
B89-X00-M03(C01)-D129	527.34	1.91	2
B89-X00-M03(C01)-D130	541.35	1.93	2
B89-X00-M03(C01)-D131	525.32	1.78	2
B89-X00-M03(C01)-D132	616.36	2.25	2
B89-X00-M03(C01)-D133	603.33	3.37	2
B89-X00-M03(C01)-D134	521.29	3.11	2
B89-X00-M03(C01)-D135	498.28	2.03	2

Ejemplo 33

1-metil-8-(pirrolidin-3-ilamino)-4,5-dihidro-1H-pirazolo [4,3- h] quinazolina-3-carboxilato de etilo [B99-X00-M00 (C01)-D03]



una solución de 110 mg (0.27 mmol) de-8-{[1-(tert-butoxicarbonil) pirrolidin-3- il] amino}-1-metil-4,5-dihidro-1H-pirazolo [4, 3-h]quinazolina-3-carboxilato de etilo en una mezcla de diclorometano-ácido trifluoroacetico 9/1 fue agitado a temperatura ambiente uno durante 6 horas. El disolvente fue entonces removido en vacío y el aceite resultante retirado con diclorometano y lavado con NaHCO3. La capa orgánica fue secada sobre Na2SO4 y evaporada. El residuo fue triturado con dietileter dando 83 mg (60 % de producción) del compuesto titulado.



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1. 98-2. 11 (m, 1 H) 2.22 (s, 1 H) 2.77 (t, J=7. 62 Hz, 2 H) 2.92-3. 02 (m, 2 H) 3.14-3.55 (m, 4H) 4.31 (s, 3H) 4.44-4.57 (m, 1 H) 7.27 (s, 2 H) 8.29 (s, 1 H) 8.76 (s, 1 H)

De manera análoga el siguiente compuesto fue preparado:

N, 1-dimetil-8-(piperidin-4-ilamino)-4,5-dihidro-1H-pirazolo [4, 3-h]quinazolina- 3-carboxamida [B79-X00-M00 (C01)-D03]

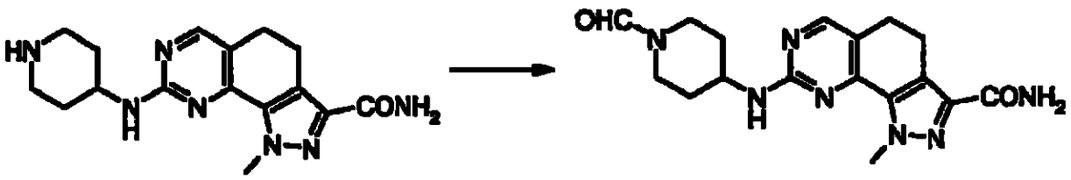
000442

442

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65-1.82 (m, 2 H) 2.05-2.16 (m, 2 H) 2.75 (d, J=4.76 Hz, 3 H) 2.75-2.80 (m, 2 H) 2.97 (t, J=7.68 Hz, 2 H) 3.01-3.09 (m, 2 H) 3.27-3.49 (m, 2 H) 3.93-4.10 (m, 1 H) 4.31 (s, 3 H) 7.59 (s, 1 H) 8.07 (q, J=4.47 Hz, 1 H) 8.26 (s, 1 H) 8.44-8.63 (m, 1 H) 8.69-8.90 (m, 1 H).

Ejemplo 34

1-metil-8-(piperidin-4-ilamino)-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3- carboxamida [B79-X00-M00 (C01)-D03]

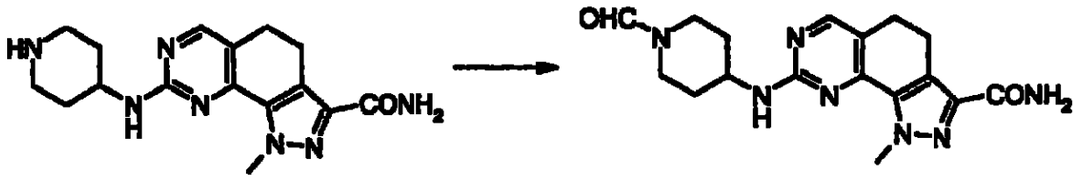


A una solución de 1 g (2.4 mmol) de 8-[(1-benzilpiperidin-4-il)amino]-1-metil-4,5- dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxamida en 90 mL de etanol absoluto 1 g de paladio sobre carbon 10 % peso y 30 ml de ácido de 98 % ácido formica fueron agregados. La mezcla resultante fue agitada a 60°C durante 12 horas. El catalizador fue entonces filtrado sobre cerita y el filtrado fue evaporado. El crudo fue purificado por cromatografía sobre columna de gel de sílice él eludió con una mezcla de CH_2Cl_2-MeOH-Et_3N, dando 350 mg (45 %de producción) del compuesto titulado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.65-1.77 (m, 2H) 2.04-2.17 (m, 2H) 2.75 (t, J=7.56 Hz, 2H) 2.96 (t, J=7. 56 Hz, 2H) 2.99-3.09 (m, 2H) 3.28-3.44 (m, 2H) 3.93- 4.08 (m, 1H) 4.31 (s, 3H) 7.25 (s, 1H) 7.31 (d, J=7. 56 Hz, 1H) 7.43 (s, 1H) 8.25 (s, 1H).

Ejemplo 35

8-[(1-formilpiperidin-4-il)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B169-X00-M00(C01)-D03



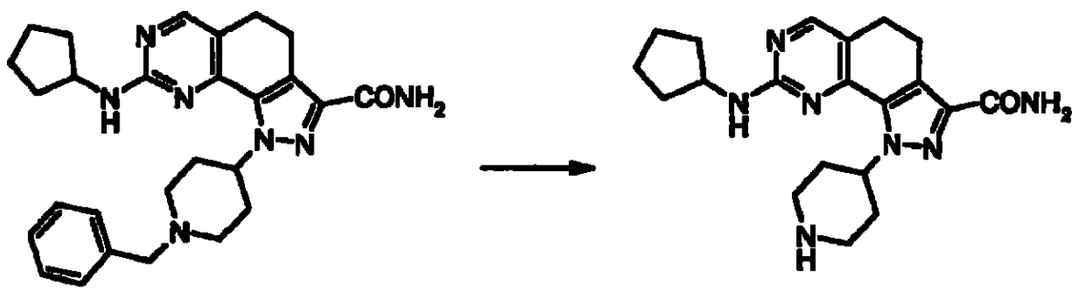
500 mg (1,53 mmol) de 1-metil-8-(piperidin-4-ilamino)-4,5-dihidro-1H-pirazolo [4,3-h]quinazolina-3-carboxamida fueron disueltos en 10 mL de dimetilformamida, que contenía 253 mg (1,68 mmol) de cloruro tert-butildimetilsililo, 0,26 mL de trietilamina y 7 mg de 4-dimetilaminopiridina (0,06 mmol), y la mezcla fue agitada a 35-40°C durante 25 horas bajo nitrógeno. La mezcla fue entonces particionada entre diclorometano y agua, la capa fue lavada con salmuera y

secada sobre sulfato de sodio. La evaporación de los volátiles en vacío proporcionó 435 mg (80% de producto) del compuesto titulado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,25-1,48(m, 2 H) 1,88-2,03 (m, 2 H) 2,74 (t, J=7,68 Hz, 2 H) 2,77-2,87 (m, 1 H) 2,95 (t, J=7, 62 Hz, 2 H) 3,10-3,20 (m, 1 H) 3,66- 3,79 (m, 1 H) 3,93-4,05 (m, 1 H) 4,09-4,17 (m, 1 H) 4,31 (s, 3 H) 7,13 (d, J=6,83 Hz, 1 H) 7,23 (s, 1 H) 7,44 (s, 1 H) 8,01 (s, 1 H) 8,23 (s, 1 H).

Ejemplo 36

8-(ciclopentilamino)-1-piperidin-4-il-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina- 3-carboxamida [B73-XOO-MOO(C18)-D03]

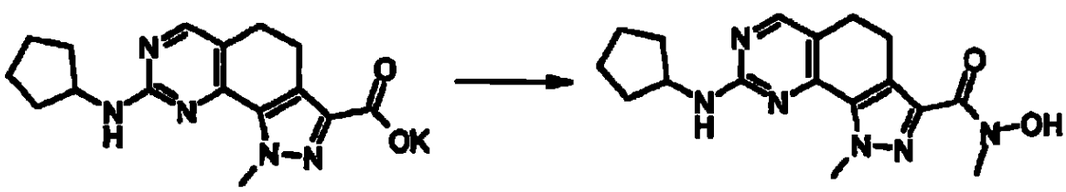


500 mg (1.1 mmol) de 1-(1-benzilpiperidin-4-il)-8-(ciclopentilamino)-4.5-dihidro-1H-pirazolo[4.3-h]quinazolina-

3-carboxamida Fueron disueltos en 50 mL de acido acetico y 50 mg de PtO_2 Fueron agregados. La mezcla fue sometida a hidrogenacion a 60 psi a temperatura ambiente.Despues de 12 horas el catalizador fue filtrado sobre celita y el filtrado evaporado. El residuo fue redisuelto con diclorometano y lavado con $NaHCO_3$ acuoso. La capa orgánica fue secada sobre sulfato de sodio y el disolvente removido bajo presión reducida El compuesto titulado (80% de producto) fue recolectado por filtración después de trituración con dietileter.

EJEMPLO 37

8- (ciclopentilamino)-N-hidroxi-N, 1-dimetil-4, 5-dihidro-1H-pirazolo [4,3- h] quinazolina-3-carboxamida [B73-X00-M00 (C01)-D142]



A Una suspensión de 400 mg (1.14 mmol)de 8(ciclopentilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de potasio- en 80 mL de diclorometano y unas pocas gotas de dimetilformamida 0.11 mL (0.13 mmol) de

cloruro de oxalilo fueron agregados a 0°C. La mezcla fue agitada a temperatura ambiente durante 6 horas y luego evaporada, redisuelta en diclorometano anhidros y invertida en una solución de 344 mg (2.28 mmol) de clorhidrato de N-metilhidroxilamina y 0.33 mL de trietilamina en 20 mL del mismo disolvente, enfriado a 0°C. Después de 4 horas la mezcla fue lavada con una solución saturada de hidrogencarbonato de sodio, secada sobre sulfato de sodio y evaporada hasta secados. El residuo fue triturado con dietileter y fue filtrado para dar 780 mg (60 % de producto) del compuesto titulado

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.46-1.61 (m,4 H) 1.64-1.78 (m, 2 H) 1.87-2.01 (m,2 H) 2.67-2.89 (m,4 H) 3.35 (s,3 H) 4.11-4. 23 (m, 1 H) 4.31 (s, 3 H) 7.06 (d, J=6. 58 Hz,1 H) 8.20 (s, 1 H) 9.88 (s, 1 H).

De manera análoga, pero empleando los derivados de hidroxilamino adecuados, los siguientes compuestos fueron preparados:

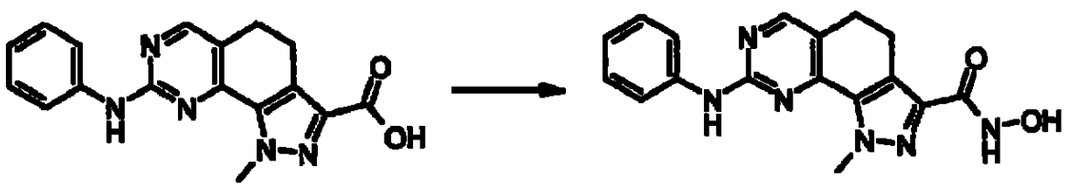
N-ciclohexil-8-(ciclopentilamino)-N-hidroxi-1-metil-4,5-dihidro-1H- pirazolo [4,3-h] quinazolina-3-carboxamida [B73-X00-M00 (CO1)-D29] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.96-2.04

(m, 18 H) 2.67-2.81 (m, 4 H) 4.04- 4.45 (m, 2 H) 4.30 (s, 3 H) 6.97-7.10 (m, 1 H) 8.20 (s, 1 H) 9.45 (s, 1 H);

N-benzil-8-(ciclopentilamino)-N-hidroxi-1-metil-4,5-dihidro-1H-pirazolo [4,3- h] quinazolina-3-carboxamida [B73-X00-M00 (C01)-D28] ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51-1.61 (m, 4 H) 1.64-1.79 (m, 2 H) 1.87- 2.00 (m, 2 H) 2.70-2.88 (m, 4 H) 4.08-4.22 (m, 1 H) 4.31 (s, 3 H) 5.01 (s, 2 H) 7.06 (d, J=6.58 Hz, 1 H) 7.22-7.43 (m, 5 H) 8.21 (s, 1 H) 9.89 (s, 1H).

EJEMPLO 38

8-anilino-N-hidroxi-1-metil-4,5-dihidro-1H-pirazolo[4,3-h] quinazolina-3- carboxamida [B04-X00-M00 (C01)-D05]



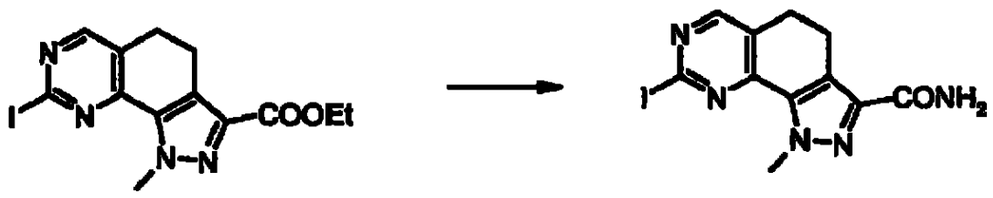
A una solución de 260 mg (0.81 mmol) de 8-anilino-1-metil-4, 5-dihidro-1H- pirazolo[4,3-h] quinazolina-3-acido carboxilico en 50 mL de dimetilformamida 111 mg de N-hidroxibenzotriazol (0.81 mmol), 0.16 mL de N- metilmorpholina, 205 mg (1.07 mmol) de clorhidrato N-(3-dimetilaminopropil)-N'-etilcarbodiimida y 585 mg (2.13 mmol) de

triphenilmetilhidroxilamina fueron agregados consecutivamente. Después de 48 horas a temperatura ambiente el disolvente fue removido bajo presión reducida y el residuo fue retirado con diclorometano y lavado con agua. La capa orgánica fue entonces sacada sobre sulfato de sodio y evaporada. El crudo fue tratado con 10 mL de una mezcla de diclorometano-ácido trifluoroacético después de 4 horas los volátiles fueron removidos en vacio. El residuo fue redisuelto con diclorometano y lavado con $NaHCO_3$ acuoso y el producto fue purificado por cromatografía sobre columna de gel de sílice, eluido con CH_2Cl_2-CH_3COCH_3 4/1, para dar 180 mg (66 % del producto) del compuesto titulado.

^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 2.80-2.91 (m, 2 H) 2.93-3.06 (m, 2 H) 4.33 (s, 3 H) 6.97 (tt, J=7.35, 1.07 Hz, 1 H) 7.31 (dd, J=8.47.7.38 Hz, 2 H) 7.72 (dd, J=8.66, 1.10 Hz, 2 H) 8.42 (s, 1 H) 8.91 (s, 1 H) 9.52 (s, 1 H) 10.93 (s, 1 H)

EJEMPLO 39

8-yodo-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxamida [B73-X00-M00 (C01)-D03]

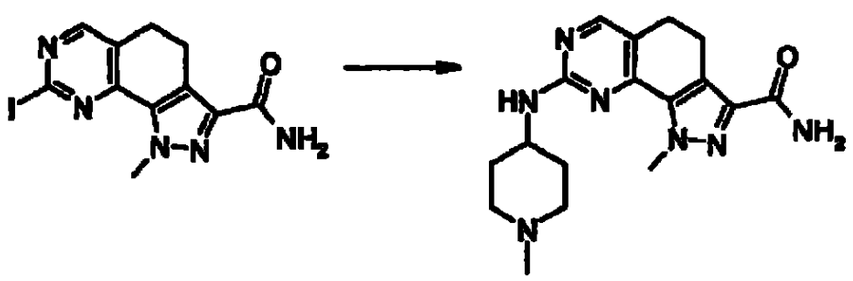


1.0 g (2.6 mmol) de 8-yodo-1-metil-4, 5-dihidro-1H-pirazolo [4,3-h] quinazolina- 3-carboxilato de etilo fueron disueltos en una mezcla de 100 mL de metanol y 100 mL de hidrato de amoniaco 33%. La solución fue agitada en una botella cerrada a 60°C durante 4 horas. El precipitado resultante fue recolectado dando 0.5 g (54% de producto) del compuesto titulado.

^{1}HNMR (400 MHz, DMSO-d_6) δ ppm 2.99 (m, 4 H) 4.25 (s, 3 H) 7.31 (s, 1 H) 7.51 (s, 1 H) 8. 47 (s, 1 H)

EJEMPLO 40

1-metil-8- [(1-metilpiperidin-4-il) amino]-4, 5-dihidro-1H-pirazolo [4,3- h] quinazolina-3-carboxamida [B90-X00-M00 (C01)-D03]

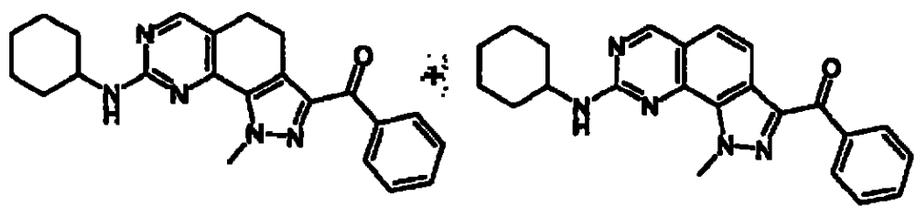


8-yodo-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxamida (0.10 g,0.28 mmol) y 1-metilpiperidin-4-amina (0.19 g, 1.7 mmol) Fueron calentados a 80°C bajo nitrógeno durante 3 horas. La mezcla fue concentrada bajo presión reducida y el residuo fue purificado por cromatografía sobre columna de gel de sílice (eluente: diclorometano/etanol/hidroxido de amoniaco 90/10/1) para dar 0.047 mg de 1-metil- 8- [(1-metilpiperidin-4-il) amino]-4, 5-dihidro-1H-pirazolo [4,3-h] quinazolina-3- carboxamida (50% de producto).

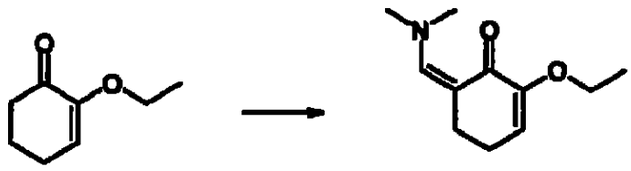
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 2 H) 1.91 (m, 2 H) 2.06 (m, 2 H) 2.4 (s, 3 H) 2.73 (m, 2 H) 2.83 (m, 2 H) 2.94 (m, 2 H) 3.70 (m, 1 H) 4.30 (s, 3 H) 7.01 (m, 1 H) 7.25 (s, 1 H) 7.44 (s, 1 H) 8.29 (s, 1 H)

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[8-(ciclohexilamino)-1-metil-4,5-dihidro-1H-pirazolo [4, 3-h]quinazolin-3- il] (fenil) metanona [B27-X00-M01 (C01)-D07] y**[8-(ciclohexilamino)-1-metil-1H-pirazolo [4,3-h] quinazolin-3-il] (fenil) metanona** [B27-X00- M01 (C01)-D07]

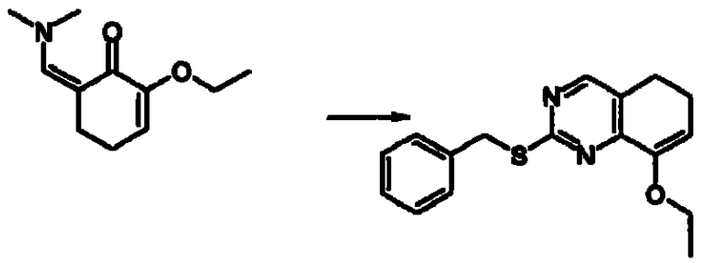


ETAPA 1 **6-[(dimetilamino)metileno]-2-etoxiciclohex-2-en-1-ona**



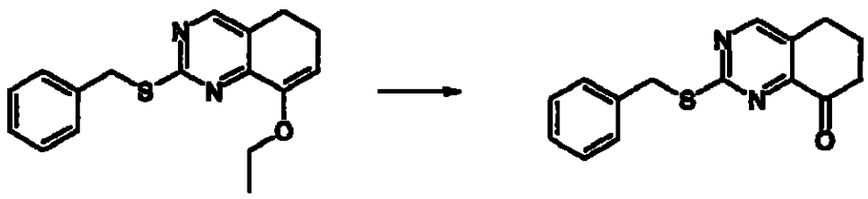
3.4 g (0.02 mmol) de 2-etoxiciclohex-2-en-1-ona Fueron disueltos en 30 mL de dimetilformamida seca y 30 mL (0.05 mmol) de acetato de dimetilformamida de dimetilo fueron agregados. La solución fue agitada a 60°C durante de 2 horas. El disolvente fue entonces evaporado bajo vació, el residuo triturado con dietileter y recolectado por filtración para 6.6 g del compuesto titulado (80% del producto).

Step 2. 2- (benziltio)-8-etoxi-5, 6-dihidroquinazolina



A una solución de 2.0 g (0.01 mol) de 6-[(dimetilamino) metileno] -2-etoxiciclohex- 2-en-1-one en 20 mL de dimetilformamida,2.6 g de S-benzilisotiourea (2 eq. mol.) fueron agregados. La mezcla de reacción fue agitada a 95°C durante 4 horas. El disolvente fue entonces evaporado bajo presión reducida y el crudo purificado por cromatografía sobre columna de gel de sílice (eluente diclorometano/metanol 9/1) llevando 1.5 g (50% de producto) del compuesto titulado.

Step 3. **2-(benziltio)-6,7-dihidroquinazolin-8 (5 H)-ona**

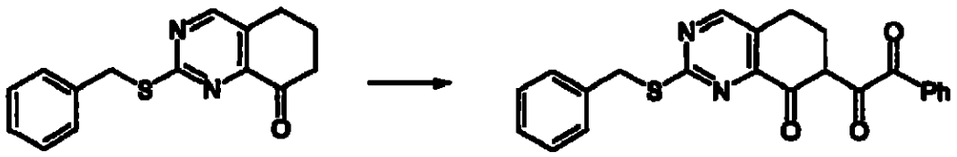


1.5 g (5 mmol) de 2-(benziltio)-8-etoxi-5,6-dihidroquinazolina Fueron disueltos en 50 mL de ácido acético y 3 mL de agua. La solución fue agitada a temperatura de reflujo durante 4 horas. El disolvente fue entonces removido

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bajo vacío, el residuo, particionado entre diclorometano y una solución saturada de $NaHCO_3$. La capa orgánica fue secada sobre Na_2SO_4 anhidro y concentrada dando 1.0 g (74% de producto) del compuesto titulado.

Etapa4.1-[2-(benziltio)-8-oxo-5,6,7, 8-tetrahidroquinazolin-7-il]-2-pheniletano- 1,2-diona



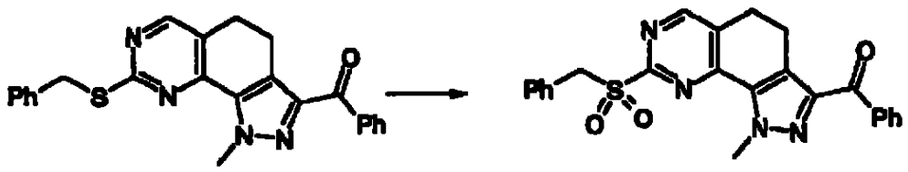
A una solución de 0.22 g (0.81 mmol) de 2-(benziltio)-6, 7-dihidroquinazolin-8 (5 H)-ona en 5 mL de tetrahidrofurano seco enfriado a -50°C, 0.10 g de hidruro de sodio 60% en aceite mineral fue agregado. La suspensión resultante fue mantenida a la misma temperatura durante 30 minutos y luego se agrego 0.59 mL de a-oxobenzenoacetato de etilo (PhCOCOOEt) y la mezcla de reacción se le permitió llegar a temperatura ambiente. Después de 16 horas la mezcla fue particionada entre agua acetato de etilo y la capa orgánica fue secada sobre Na_2SO_4 y evaporada hasta secado. El residuo fue purificado por cromatografía sobre columna de gel de sílice (eluente hexano/acetato de etilo 7/3) dando 0.22 g (68% de producto) del compuesto titulado.

Etapa 5. [8-(benziltio)-1-metil-4,5-dihidro-1H-pirazolo [4,3-h] quinazolin-3-il] (penil) metanona [B05-X04-M00 (C01)-D07]



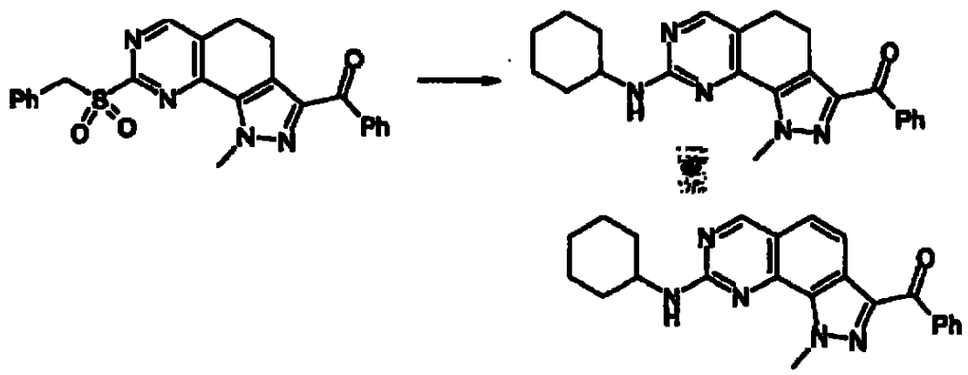
0.22 g (0.55 mmol) de 1-[2-(benziltio)-8-oxo-5,6,7,8-tetrahidroquinazolin-7-il]-2-feniletano-1,2-diona se disolvieron en 6 mL de etanol y se agregaron 0.03 g (0.66 mmol) de metil hidrazina. La mezcla de reacción se mantuvo bajo agitación a temperatura de reflujo durante 5 horas. Después de ese tiempo el disolvente se removió bajo presión reducida, el residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4 y se concentró, dando 0.16 g del compuesto del título (70% de producto).

Etapa 6. [8-(benzilsulfonil)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h] quinazolin-3-il] (fenil) metanona [B05-X05-M00(C01)-D07]



A una solución de 70 mg (0.17 mmol) de [8-(benziltio)-1-metil-4,5-dihidro-1H- pirazolo[4,3-h] quinazolin-3-il] (fenil) metanona en 3 mL de diclorometano, se agregaron 115 mg (0.34 mmol) de ácido m-cloroperbenzoico. La mezcla de reacción se mantuvo a temperatura ambiente durante 1 hora. La solución luego se lavó con $NaHCO_3$ acuoso y la capa orgánica se secó sobre Na_2SO_4 y se evaporó en vacío, dando 70 mg (93% de producto) del compuesto del título.

Etapa 7. [8-(ciclohexilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolin-3-il](fenil)metanona [B27-X00-M00(C01)-D07] **y [8-(ciclohexilamino)-1-metil-1H-pirazolo[4,3-h]quinazolin-3-il](fenil)metanona** [B27-X00- MOI (C01)-D07]



000456
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83 mg (0.19 mmol) de [8-(benzilsulfonil)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolin-3-il](fenil)metanona se disolvieron en 3 mL de dimetilsulfóxido y ciclohexilamina (0.033mL, 0.29 mmol) y la solución se calentó a 100°C bajo agitación durante 16 horas. El disolvente luego se removió bajo presión reducida y el crudo se purificó mediante cromatografía sobre columna de gel de sílice (eluente diclorometano/acetona) dando 31 mg de [8-(ciclohexilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolin-3-il](fenil) metanona y 15 mg de [8-(ciclohexilamino)-1-metil-1H-pirazolo[4,3-h]quinazolin-3-il](fenil)metanona (70% de producto en general).

B27-X00-M00(C01)-D07

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.00-2.00 (5m, 11 H) 2.61 (m, 2 H) 2.66 (m, 2 H) 3.80 (s, 3 H) 7.17 (bs, 1 H) 7.34-7.37 (m, 3 H) 7.41-7.51 (m, 3 H) 8.27 (s, 1 H);

B27-X00-M01 (C01)-D07

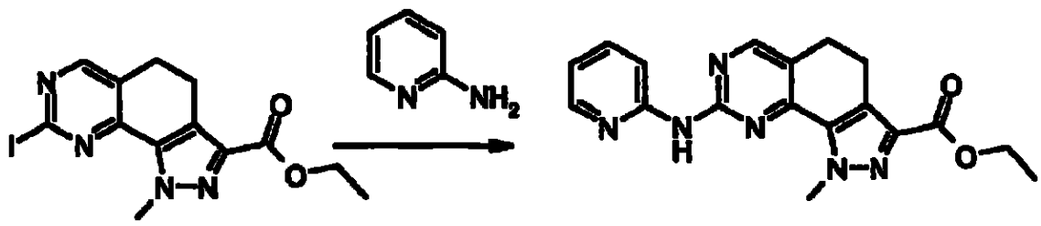
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20-2.20 (5m, 11 H) 4.02 (bs, 3 H) 6.69 (m, 1 H) 7.37-7.58 (2m, 6 H) 7.93 (bs, 1 H) 8.83 (bs, 1 H).

Ejemplo 42

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1-metil-8-(piridin-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B15-X00-M00(C01)-D01]



Acetato de paladio [$Pd(OAc)_2$] (15.3 mg, 0.07 mmol, 10%), (±)-BINAP (42.6 mg, 0.07 mmol, 10%) y dimetilformamida (12 mL) se cargaron en un frasco de fondo redondo lavado con argón. La mezcla se agitó bajo argón durante 30 minutos. Luego se agregaron 2-aminopiridina (70.4 mg, 0.75 mmol), etil 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato (250 mg, 0.65 mmol), carbonato de potasio (1.89 g, 13.67 mmol) y dimetilformamida (5 mL). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y luego se calentó a 120°C en un baño de aceite bajo argón con buena agitación durante 18 horas.

Después de enfriar a temperatura ambiente, la mezcla de reacción se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se lavaron con solución salina y se secaron sobre Na_2SO_4. El disolvente se removió bajo vacío, el

sólido crudo se retiró con dietil éter, se filtró, se lavó con dietil éter y se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 97.5:2.5) para producir 145 mg (63.8% de producto) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J7.1 Hz, 3 H) 3.0 (m, 4 H) 4.3 (q, J7.2 Hz, 2 H) 4.4 (s, 3 H) 7.0 (ddd, J7.2, 4.9, 1.0 Hz, 1 H) 7.8 (ddd, 1 H) 8.2 (d, J 8.4 Hz, 1 H) 8.3 (ddd, J4. 8, 2.0, 0.9 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H).

Al trabajar de acuerdo con el método anterior, se prepararon los siguientes compuestos:

8-[(3,5-diclorofenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B14-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, J7.2 Hz, 2H) 4.4 (s, 3 H) 7.1 (m, 1 H) 7.4 (m, 2 H) 8.5 (s, 1 H) 10 (s, 1 H);

8-{[3-metoxi-5-(trifluorometil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B16-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J7.1 Hz, 3 H) 2.9 (m, 4 H) 3.8 (s, 3 H) 4.3 (q, J 7.2 Hz, 2 H) 4.4 (s, 3 H) 6.8 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-[(4-hidroxifenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B18-X00-M00(C01) D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (m, 5 H) 6.7 (d, J 8.8 Hz, 2 H) 7.4 (d, J 8.9 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H) 9.2 (s, 1 H);

8-(1H-imidazol-1-ilamino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B21-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (m, 3 H) 2.9 (m, 4 H) 4.3 (d, J 7.1 Hz, 2 H) 4.4 (s, 3 H) 7.1 (s, 1 H) 7.6 (d, J 8.9 Hz, 2 H) 7.7 (s, 1 H) 7.9 (d, 78. 9 Hz, 2 H) 8.2 (s, 1 H) 8.5 (s, 1 H) 9.7 (s, 1 H);

1-metil-8-(1,3-tiazol-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B86-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (m, 3 H) 3.0 (m, 4 H) 4.3 (q, J7.1 Hz, 2 H) 4.4 (s, 3 H) 7.1 (d, J3.5 Hz, 1 H) 7.5 (d, J3.7 Hz, 1 H) 8.6 (s, 1 H) 11.6 (s, 1 H);

1-metil-8-(1H-pirazol-3-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B77-X00-M00(C01) D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q,. J 7.1 Hz, 2 H) 4.4 (s, 3 H) 6.5 (s, 1 H) 7.6 (s, 1 H) 8.4 (s, 1 H) 9.6 (s, 1 H) 12.2 (s, 1 H);

1-metil-8-[(4-morfolin-4-ilfenil)amino]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B19-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 3.1 (m, 4 H) 3.8 (m, 4 H) 4.3 (q, J 7.2 Hz, 2 H) 4.3 (s, 3 H) 6.9 (d, J 9.0 Hz, 2 H) 7.6 (d, J 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-{[4-(etoxicarbonil)fenil]amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B87-X00-M00(C01)D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 6 H) 3.0 (m, 4 H) 4.3 (m, 4 H) 4.4 (s, 3 H) 7.9 (m, 4 H) 8.5 (s, 1 H) 10.0 (s, 1 H);

8-{[4-(N,N-dietilamino)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B17-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (t, J 7.0 Hz, 6 H) 1.3 (t, J7.1 Hz, 3 H) 2.9 (m, 4 H) 3.3 (m, 4 H) 4.3 (q, J7.1, 7.1 Hz, 2 H) 4.3 (s, 3 H) 6.7 (d, 79.1 Hz, 2 H) 7.4 (d, J 9.0 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H);

8-{[4-(acetilamino)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B22-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J7.1 Hz, 3 H) 2.0 (s, 3 H) 2.9 (m, 4 H) 4.3 (q, J7.1 Hz, 2 H) 4.4 (s, 3 H) 7.5 (d, J9.0 Hz, 2 H) 7.6 (d, J9.0 Hz, 2 H) 8.4 (s, 1 H) 9.4 (s, 1 H) 9.8 (s, 1 H);

8-{[3-(hidroximetil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B11-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, J7.1 Hz, 2 H) 4.4 (s, 3 H) 4.5 (s, 2 H) 6.9 (m, 1 H) 7.3 (t, J7.8 Hz, 1 H) 7.5 (m, 1 H) 7.8 (s, 1 H) 8.4 (s, 1-H) 9.5 (s, 1 H);

8-[(4-metoxifenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B68-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J7.1 Hz, 3 H) 2.9 (m, 4 H) 3.7 (s, 3 H) 4.3 (q, J 7.1 Hz, 2 H) 4.3 (s, 3 H) 6.9 (d, J 9.0 Hz, 2 H) 7.6 (d, J9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-{[(4-Bromo-3-cloro)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h] quinazolina-3-carboxilato de etilo [B88-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.3 (t, J 7.1 Hz, 3 H) 2.9 (m, 4 H) 4.3 (q, J 7.1 Hz, 2 H) 4.4 (s, 3H) 7.6 (dd, J8.8, 2.4 Hz, 1 H) 7.7 (d, J 8.8 Hz, 1 H) 8.2 (d, J2.4 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-{[3-bromo-5-(trifluorometil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B115-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J=7.1 Hz, 3 H) 2.95 (m, 4 H) 4.31 (q, J=7.2 Hz, 2 H) 4.39 (s, 3 H) 7.49 (s, 1 H) 8.10 (s, 1 H) 8.36 (s, 1 H) 8.54 (s, 1 H) 10.11 (s, 1 H);

8-[4-(4-metil-piperazin-1-il)-3-(hidroximetil)fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B116-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J=7.07 Hz, 3 H) 2.28 (s, 3 H) 2.42-2.61 (m, 4 H) 2.79-2.88 (m, 6 H) 2.98 (t, J=7.80 Hz, 2 H) 4.31 (q, J=7.15 Hz, 2 H) 4.36 (s, 3 H) 4.56 (d, J=5.24 Hz, 2 H) 5.06 (t, J=5.30 Hz, 1 H) 7.03 (d, J=8.66 Hz, 1 H) 7.50 (dd, 1 H) 7.81 (d, J=2.68 Hz, 1 H) 8.39 (s, 1 H) 9.42 (s, 1 H);

1-metil-8-{[4-(morfolin-4-ilmetil)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B102-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J=7.13 Hz, 3 H) 2.35 (s, 4 H) 2.86 J=7.62 Hz, 2 H) 2.99 (t, J=7.80 Hz, 2 H) 3.42

(s, 2 H) 3.55-3.61 (m, 4 H) 4.31 (q, J=7.07 Hz, 2 H) 4.37 (s, 3 H) 7.24 (d, J=8.41 Hz, 2 H) 7.66 (d, J=8.41 Hz, 2 El) 8.42 (s, 1 H) 9.52 (s, 1 H);

1-metil-8-({4-[(1-metilpiperidin-4-il)oxi]fenil}amino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B103-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (t, 3 H) 2.09 (m, 4 H) 2.86 (m, 5 H) 2.98 (t, 2 H) 3.37 (m, 5 H) 4.30 (q, 2 H) 4.34 (s, 3H) 7.03 (m, 2 H) 7.61 (m, 2 H) 8.39 (s, 1 H) 9.40 (s, 1 H);

1-metil-8-({3-[(4-metilpiperazin-1-il)metil]fenil}amino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B104-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.21 (m, 3 H) 2.40 (m, 8 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 3.44 (s, 2 H) 4.30 (q, 2 H) 4.39 (s, 3 H) 6.91 (m, 1 H) 7.24 (m, 1 H) 7.56 (m, 1 H) 7.75 (dd, 1 H) 8.43 (m, 1 H) 9.54 (s, 1 H);

8-{[3-fluoro-4-(4-metilpiperazin-1-il)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B109-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.28 (s, 3 H) 2.85 (t, 2 H) 2.99 (m, 6 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 7.01 (t, 1 H) 7.35 (dd, 1 H) 7.64 (dd, 1 H) 8.42 (m, 1 H) 9.56 (s, 1 H);

8-[(4-clorofenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B112-X00-M00(C01)-D01]

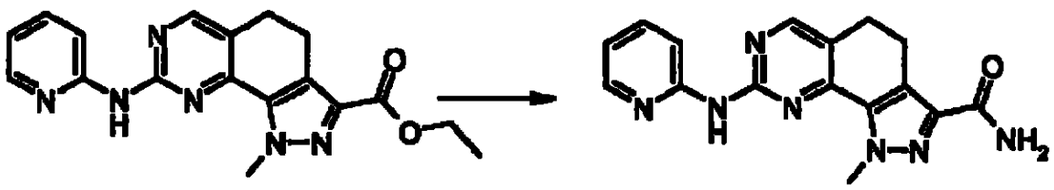
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 7.38 (d, 2 H) 7.74 (d, 2 H) 8.45 (s, 1 H) 9.70 (s, 1 H);

8-{[4-(hidroximetil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B114-X00-M00(C01)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H) 2.86 (t, 2 H) 2.99 (t, 2 H) 4.30 (q, 2 H) 4.37 (s, 3 H) 4.45 (s, 2 H) 7.27 (d, 2 H) 7.65 (d, 2 H) 8.42 (s, 1 H) 9.50 (s, 1 H).

Ejemplo 43

1-Metil-8-(piridin-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B15-X00-M00(C01)-D03]



A una solución de 1-metil-8-(piridin-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo (220 mg, 0.63 mmol) en metanol (250 mL), se agregó hidróxido de amonio acuoso al 33% (100 mL) y la solución se agitó a 65°C durante 8 horas.

Por medio de concentrar la solución, el compuesto final que se precipitó se recolectó mediante filtración y succión, se lavó con agua y se cristalizó dos veces a partir de metanol que contenía hidróxido de sodio, y se secó a 40°C bajo vacío. Así se obtuvieron 60 mg del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.0 (m, 4 H) 4.4 (s, 3 H) 7.0 (ddd, J 7.2, 4.9, 1.0 Hz, 1 H) 7.3 (s, 1 H) 7. 5 (s, 1 H) 7.8 (ddd, 1 H) 8.2 (d, J8. 4 Hz, 1 H) 8.3 (ddd, J 4.8, 2.0, 0.9 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H)

Al trabajar de acuerdo con el mismo procedimiento, se prepararon los siguientes compuestos:

8-[(3,4-diclorofenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B14-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (t, J 1.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.9 (d, J 1.8 Hz, 2 H) 8.5 (s, 1 H) 10.0 (s, 1 H);

8-{[3-metoxi-5-(trifluorometil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B16-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.8 (s, 3 H) 4.3 (s, 3 H) 6.8 (s, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (s, 1 H) 7.8 (s, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-[(4-hidroxifenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B18-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 6.7 (d, J 8.8 Hz, 2 H) 7.2 (s, 1 H) 7.4 (d, J 8.9 Hz, 2 H) 7.5 (s, 1 H) 8.3 (s, 1 H) 9.1 (s, 1 H) 9.2 (s, 1 H);

8-{[4-(1H-imidazol-1-il)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B21-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.4 (s, 3 H) 7.1 (s, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, J8. 9 Hz, 2 H) 7.7 (t, J 1.2 Hz, 1 H) 7.9 (d, J9.0 Hz, 2 H) 8.2 (s, 1 H) 8.4 (s, 1 H) 9.7 (s, 1 H);

1-metil-8-(tiazol-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B86-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (d, J3.7 Hz, 1 H) 7.3 (s, 1 H) 7.5 (d, J 3.7 Hz, 1 H) 7.5 (s, 1 H) 8.6 (s, 1 H) 11.8 (s, 1 H);

1-metil-8-(1H-pirazol-3-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B77-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 6.5 (bs, 1 H) 7.25 (s, 1 H) 7.45 (s, 1 H) 7.6 (bs, 1 H) 8.4 (s, 1 H) 9.9 (s, 1 H);

8-{[4-(N-morfolino)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B19-X00-M00 (C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.1 (m, 4 H) 3.8 (m, 4 H) 4.3 (s, 3 H) 6.9 (d, J 9.1 Hz, 2 H) 7.2 (s, 1 H) 7.5 (s, 1 H) 7.6 (d, J 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-{[4-(dietilamino)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B17-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (t, J 7.0 Hz, 6 H) 2.9 (m, 4 H) 3.3 (m, 4 H) 4.3 (s, 3 H) 6.7 (d, J9.0 Hz, 2 H) 7.2 (s, 1 H) 7.4 (m, J9.0 Hz, 1 H) 7.4 (d, J9.0 Hz, 2 H) 8.3 (s, 1 H) 9.1 (s, 1 H);

8-{[4-(acetilamino)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B22-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.9 (m, 4 H) 4.3 (s, 3 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (d, J8.9 Hz, 2 H) 7.6 (d, J9.0 Hz, 2 H) 8.4 (s, 1 H) 9.4 (s, 1 H) 9.8 (s, 1 H);

8-{[3-(hidroximetil)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B11-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.3 (s, 3 H) 4.5 (s, 2 H) 5.2 (s, 1 H) 6.9 (d, J8.0 Hz, 1 H) 7.2 (m, 2 H) 7.5 (s, 1 H) 7.5 (dd, J 8.1, 1.4 Hz, 1 H) 7.8 (t, J 1.8 Hz, 1 H) 8.4 (s, 1 H) 9.5 (s, 1 H);

8-[(4-metoxifenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B68-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d) δ ppm 2.9 (m, 4 H) 3.7 (s, 3 H) 4.3 (s, 3 H) 6.9 (d, J 9.1 Hz, 2 H) 7.3 (s, 1 ET) 7.5 (s, 1 H) 7.6 (d, J 9.0 Hz, 2 H) 8.4 (s, 1 H) 9.3 (s, 1 H);

8-{[(4-Bromo-3-cloro)fenil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B88-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 4.4 (s, 3 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, J8. 8,2.4 Hz, 1 H) 7.7 (d, J8.8 Hz, 1 H) 8.2 (d, J2.4 Hz, 1 H) 8.5 (s, 1 H) 9.9 (s, 1 H);

8-[4-(4-metil-piperazin-1-il)-3-(hidroximetil) fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B116-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.29 (s, 3 EI) 2.45-2.61 (m, 4 H) 2.73-2.87 (m, 6 H) 2.99 (t, J=7.56 Hz, 2 H) 4.34 (s, 3 H) 4.56 (d, J=5.24 Hz, 2 H) 5.06 (t, J=5.37 Hz, 1 H) 7.03 (d, J=8.66 Hz, 1 H) 7.26 (s, 1 H) 7.46 (s, 1 H) 7.50 (dd, J=8.23, 2.99 Hz, 1 H) 7.83 (d, J=2.68 Hz, 1 H) 8.38 (s, 1 H) 9.40 (s, 1 H);

Metil amida de ácido 8-[4-(4-metil-piperazin-1-il)-3-(hidroximetil)fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B116-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.45-2.55 (m, 4 H) 2.75 (d, J=4.63 Hz, 3 H) 2.81 (t, J=7.19 Hz, 2 H) 2.83 (t, J=4.63 Hz, 4 H) 2.99 (t, J=7.56 Hz, 2 H) 4.34 (s, 3 H) 4.56 (d, J=5.24 Hz, 2 H) 5.05 (t, J=5.37 Hz, 1 H) 7.03 (d, J=8.54 Hz, 1 H) 7.50 (d, J=8.41, 2.56 Hz, 1 H) 7.83 (d, J=2.68 Hz, 1 H) 8.07 (q, J=4.63 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H);

Triclorhidrato de 8-[4-(4-metil-piperazin-1-il)-3-(bromo)fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B117-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 2.88 (d, J=4.68 Hz, 3 H) 3.01 (m, 4 H) 3.19 (m, 2 H) 3.53 (m, 2 H) 4.37 (s, 3 H) 7.23 (m, 1 H) 7.29 (s, 1 H) 7.46 (s, 1 H) 7.63 (m, 1 H) 8.21 (m, 1 H) 8.44 (s, 1 H) 9.67 (s, 1 H) 10.13 (s, 1 H);

8-[3-(4-metil-piperazin-1-ilmetil)-fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B104-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.44 (s, 4 H) 2.78-3.03 (m, 4 H) 3.04-3.40 (m, 4 H) 3.45 (s, 2 H) 4.37 (s, 3 H) 6.90 (d, J=7.32 Hz, 1 H) 7.25 (t, J=7.68 Hz, 1 H) 7.27 (s, 1 H) 7.46 (s, 1 H) 7.57 (dd, J=7.68, 1.59 Hz, 1 H) 7.76 (t, J=1.77 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H);

8-{[(3-hidroxi)-5-trifluorometil]fenilamino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B118-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.77-3.07 (m, 4 H) 3.84 (s, 3 H) 4.35 (s, 3 H) 6.84 (s, 1 H) 7.28 (s, 1 H) 7.47 (s, 1 H) 7.57 (s, 1 H) 7.85 (s, 1 H) 8.49 (s, 1 H) 9.86 (s, 1 H);

Metilamida de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h] quinazolina-3-carboxílico [B10-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (d, J=4.76 Hz, 3 H) 2.81 (t, J=7.68 Hz, 2 H) 2.85 (d, J=4.39 Hz, 3 H) 2.94-3.07 (m, 4 H) 3.11-3.25 (m, 2 H) 3.51 (d, J=11.83 Hz, 2 H) 3.73 (d, J=13.66 Hz, 2 H) 4.33 (s, 3 H) 6.99 (d, J=9.15 Hz, 2 H) 7.60 (d, J=9.02 Hz, 2 H) 8.08 (q, J=4.67 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H) 10.36 (s, 1 H);

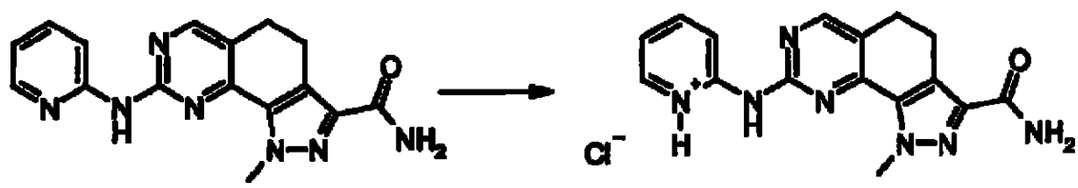
Metilamida de ácido 8-anilino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B04-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, J=4.76 Hz, 3 H) 2.79 (t, J=7.68 Hz, 2 H) 2.97 (t, J=7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, J=7.38 Hz, 1 H) 7.21-7.32 (m, 2 H) 7.68 (d, J=7.56 Hz, 2 H) 8.06 (q, J=4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H).

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Ejemplo 44

Clorhidrato de 1-Metil-8-(piridin-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida



A una solución de 1-metil-8-(piridin-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida en una mezcla 1:1 de metanol y diclorometano, se agregó HCl al 4N en dioxano (1 mL). Después de 1 hora a temperatura ambiente el disolvente se removió bajo vacío y el sólido se trituró con dietil éter proporcionando el compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.3 (m, 2 H) 7.5 (s, 1 H) 7.8 (d, J 8.8 Hz, 1 H) 8.2 (t, J 7.7 Hz, 1 H) 8.4 (dd, J 5.9, 1.0 Hz, 2 H) 8.6 (s, 1 H) 11.6 (s, 1 H).

Al trabajar de acuerdo con este método, se prepararon los siguientes compuestos:

Clorhidrato de 1-metil-8-(tiazol-2-ilamino)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.0 (m, 4 H) 4.4 (s, 3 H) 7.1 (d, J 3.7 Hz, 1 H) 7.3 (s, 1 H) 7.5 (d, J 3.7 Hz, 1 H) 7.5 (s, 1H) 8.6 (s, 1H) 11.8 (s, 1 H);

Triclorohidrato de 8-[4(N-Metilpiperazino)-3-clorofenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.1 (m, 15 H) 4.4 (s, 3 H) 7.2 (d, J 8.9 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, J 8.8, 2.4 Hz, 1 H) 8.0 (d, J 2.6 Hz, 1 H) 8.4 (s, 1 H) 9.7 (s, 1 H) 10.5 (s, 1 H);

Triclorohidrato de 8-[4(N-Metilpiperazino)-3-bromofenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.1 (m, 15 H) 4.4 (s, 3 H) 7.2 (d, J 8.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.6 (dd, J 8.6, 2.4 Hz, 1 H) 8.0 (d, J2.6 Hz, 1 H) 8.2 (s, 1 H) 9.7 (s, 1 H) 10.5 (s, 1 H);

(L) -tartrato de N-bencil-1-metil-8-{[4-(4-Metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H) 2.70 (m, 4 H) 2.80 (t, J=7.62 Hz, 2 H) 3.00 (t, J=7.62 Hz, 2 H) 3.14 (m, 4 H) 4.20 (s, 2 H) 4.34 (s, 3 H) 4.43 (d, J=6.34 Hz, 2 H) 6.93 (d, J=9.15 Hz, 2 H) 7.27 (m, 5 H) 7.55 (d, J=90.02 Hz, 2 H) 8.35 (s, 1 H) 8.69 (t, J=6.34 Hz, 1 H) 9.28 (s, 1 H);

Clorhidrato de 1-metil-8-[(4-morfolin-4-ilfenil)amino]-N-[(1R)-1-feniletil]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.97 (m, 4 H) 3.21 (m, 4 H) 3.84 (m, 4 H) 4.37 (m, 3 H) 5.15 (m, 1 H) 7.28 (m, 7 H) 7.63 (m, 2 H) 8.40 (m, 1 H) 8.44 (m, 1 H) 9.50 (m, 1 H);

Clorhidrato de N-(3-fluorobencil)-1-metil-8-[(4-morfolin-4-ilfenil)amino]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

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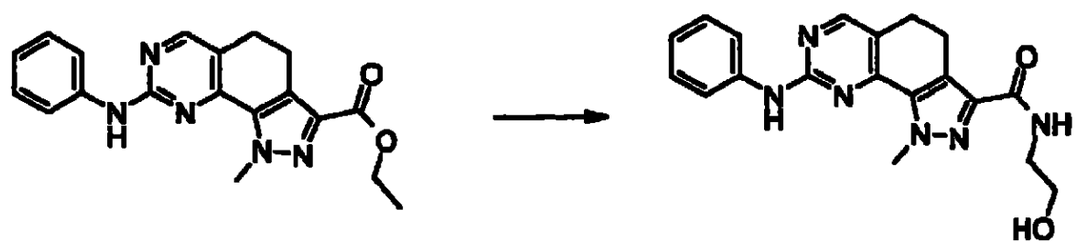
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (m, J=73.53 Hz, 4 H) 3.16 (m, 4 H) 3.81 (m, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 7.07 (m, 6 H) 7.61 (m, 2 H) 8.37 (m, 1 H) 8.80 (m, 1 H) 9.44 (m, 1 H);

Metanosulfonato de N-(3-fluorobenzil)-1-metil-8-[(4-morfolin-4-ilfenil)amino]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 3.00 (s, 4 H) 3.17 (s, 4 H) 3.80 (s, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 7.07 (m, 6 H) 7.61 (m, 2 H) 8.37 (m, 1 H) 8.80 (m, 1 H) 9.46 (m, 1 H).

Ejemplo 45

8-anilino-N-(2-hidroxietil)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B04-X00-M00(C01)-D06]



A una suspensión de 0.30 g (0.86 mmol) de 8-anilino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo en una mezcla de 10 mL de metanol y 10 mL de dimetilformamida, se agregaron 5 mL de etanolamina. La mezcla se calentó en una botella cerrada bajo agitación a 65 °C. Después de 5 horas el disolvente se removió, el residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4 y se evaporó. El residuo se trituró con dietil éter y el producto se recolectó mediante filtración (60 % de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.7-3.0 (2m, 4 H) 3.47 (m, 4 H) 4.32 (s, 3 H) 4.71 (t, 1 H) 6.94-7.67 (3m, 5 H) 7.91 (t, J 5.73 Hz, 1 H) 8.38 (bs, 1 H) 9.48 (bs, 1 H).

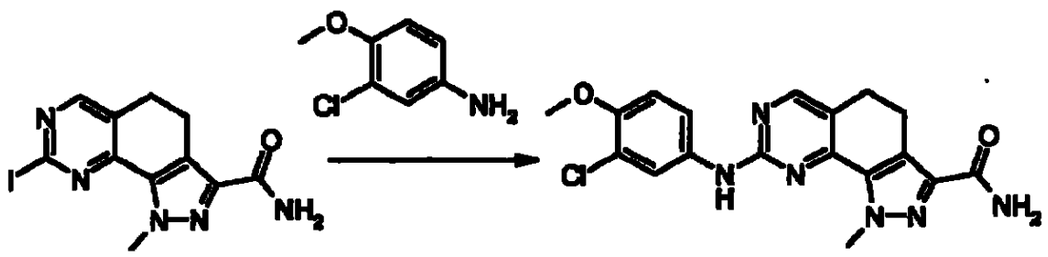
Al trabajar análogamente se preparó el siguiente compuesto:

8-anilino-N,1-dimetil-4,5-dihidro-1H-pirazolo[4,3-h] quinazolina-3-carboxamida [B04-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, J4.76 Hz, 3 H) 2.79 (t, J 7.68 Hz, 2 H) 2.97 (t, J7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, J7.38 Hz, 1 H) 7.28 (m, 2 H) 7.68 (d, J 7.56 Hz, 2 H) 8.06 (q, J 4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H).

Ejemplo 46

8-[(4-metoxi-3-clorofenil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B20-X00-M00(C01)-D03]



$Pd(OAc)_2$ (20 mg, 0.09 mmol, 10%), (±)-BINAP (55 mg, 0.09 mmol, 10%) y dimetilformamida (15 mL) se cargaron en un frasco de fondo redondo lavado con argón. La mezcla se agitó bajo argón durante 30 minutos. Luego se agregaron 3-cloro-p-anisidina (153 mg, 0.97 mmol), 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida (300 mg, 0.84 mmol), K_2CO_3 (2.45 g, 17.8 mmol) y dimetilformamida (6 mL). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y luego se calentó a 120°C en un baño de aceite bajo argón con buena agitación durante 18 horas.

Después de enfriar a temperatura ambiente, la mezcla de reacción se vertió en agua (300 mL) y se extrajo con diclorometano (5 x 60 mL). Los extractos orgánicos se lavaron

con agua (2 x 20 mL) y se secaron sobre Na_2SO_4 anhidro. El disolvente se removió bajo vacío, el sólido crudo se retiró con dietil éter, se filtró, se lavó con dietil éter y se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 97.5:2.5) para producir 95 mg de compuesto del título puro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.9 (m, 4 H) 3.8 (s, 3 en 4.3 (s, 3 H) 7.1 (d, J 9.0 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (dd, J9.0, 2.6 Hz, 1 H) 7.9 (d, J2. 6 Hz, 1 H) 8.4 (s, 1 H) 9.5 (s, 1 H).

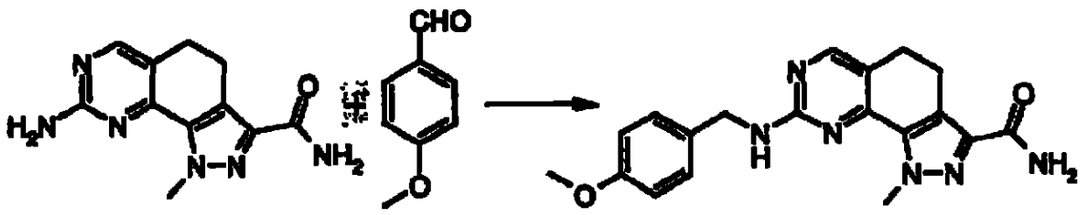
Al trabajar de acuerdo con el mismo procedimiento se preparó el siguiente compuesto:

8-[4(N-Metil-N-piperazinil)-3-clorofenilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B13-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.3 (s, 3 H) 2.5 (m, 4 H) 2.9 (m, 8 H) 4.4 (s, 3 H) 7.1 (d, J 8.8 Hz, 1 H) 7.3 (s, 1 H) 7.5 (s, 1 H) 7.5 (dd, J 8.8, 2.4 Hz, 1 H) 8.0 (d, J2.6 Hz, 1 H) 8.4 (s, 1 H) 9.6 (s, 1 H).

Ejemplo 47

8-[(4-metoxibenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B60-X00-M00(C01)-D03]



A una solución de 8-amino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida (244 mg, 1.0 mmol) en una mezcla de ácido acético glacial/metanol/agua (1:1:1) (30 mL) en un frasco de fondo redondo se agregó p-metoxibenzaldehido (0.44 mL, 450 mg, 3.0 mmol) y luego cianoborohidruro de sodio al 85% (210 mg, 2.0 mmol). La solución se agitó a temperatura ambiente durante 7 horas. En ese momento una cantidad adicional de aldehido (0.44 mL) y cianoborohidruro de sodio (210 mg) se agregaron y la agitación continuo durante la noche.

La mezcla de reacción se vertió en agua con hielo (200 mL), el pH se ajustó a 10 mediante adición de crbonato de sodio saturado y la solución se extrajo con acetato de etilo (4 x 20 mL). Los extractos orgánicos recolectados se lavaron con

solución salina hasta que se neutralizaron, con agua y se secaron sobre Na_2SO_4.

La evaporación del disolvente bajo vacío dejó un residuo sólido amarillo que se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 95:5) para proporcionar 250 mg de compuesto puro amarillo. La cristalización a partir del metanol proporcionó 225 mg del compuesto del título cristalino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 3.7 (s, 3 H) 4.2 (s, 3 H) 4.5 (d, J 6.1 Hz, 2 H) 7. 2 (s, 1 H) 6.8 (d, J 8.8 Hz, 2 H) 7.4 (s, 1 H) 7.3 (d, J 8.8 Hz, 2 H) 7.6 (m, 1 H) 8.2 (s, 1H)

Al trabajar de acuerdo con este método, se prepararon los siguientes compuestos:

1-metil-8-[(tien-3-ilmetil)amino]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B43-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (d, J 6.1 Hz, 2 H) 7.1 (m, 1 H) 7.2 (s, 1 H) 7.3 (m, 1 H) 7.4 (s, 1 H) 7.5 (m, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H);

8-[(3,5-dihidroxibenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B62-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (m, 2 H) 4.3 (s, 3 H) 4.4 (d, J 6.2 Hz, 2 H) 6.0 (m, 1 H) 6.2 (m, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H);

8-({4-[3-(dimetilamino)propoxi]benzil}amino)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B61-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.8 (m, 2 H) 2.2 (s, 6 H) 2.4 (t, 2 H) 2.8 (m, 4 H) 4.0 (t, 2 H) 4.3 (s, 3 H) 4.5 (d, J 6.5 Hz, 2 H) 6.9 (m, J 9.0 Hz, 2 H) 7.2 (d, J 8.7 Hz, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H) H);

Acetato de [5-({[3-(aminocarbonil)-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolin-8-il]amino}metil)-2-furil]metilo [B65-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.8 (m, 4 H) 4.3 (s, 3 H) 4.5 (d, J 6.1 Hz, 2 H) 5.0 (s, 2 H) 6.2 (d, J 3.2

Hz, 1 H) 6.4 (d, J 3.2 Hz, 1 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (t, J6.0 Hz, 1 H) 8.2 (s, 1 H);

8-[(3-cianobenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B63-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.1 (s, 3 H) 4.6 (d, J6.1 Hz, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.5 (t, J7.7 Hz, 1 H) 7.7 (m, 4 H) 8.2 (s, 1 H);

8-[(4-Bromobenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B64-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (d, J 6.3 Hz, 2 H) 7.2 (s, 1H) 7.3 (d, J 8.5 Hz, 2 H) 7.4 (s, 1 H) 7.5 (d, J 8.5 Hz, 2 H) 7.7 (m, 1 H) 8.2 (s, 1 H);

8-{[4-(acetilamino)benzil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B80-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.0 (s, 3 H) 2.7 (m, 2 H) 2.9 (t, J 7.7 Hz, 2 H) 4.2 (s, 3 H) 4.5 (d, J 6.2 Hz, 2 H) 7.2 (s, 1 H) 7.3 (d, J 8.5 Hz, 2 H) 7.4 (s, 1 H) 7.5 (d, J 8.5 Hz, 2 H) 7.6 (t, J7.4 Hz, 1 H) 8.2 (s, 1 H) 9.9 (s, 1 H);

B81-X00-M00(C01)-D03

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.7 (m, 2 H) 2.9 (t, J7.6 Hz, 2 H) 4.3 (s, 3 H) 4.3 (s, 2 H) 4.5 (d, J6.0Hz, 2H) 5.1 (s, 1 H) 6.2 (m, 2 H) 7.2 (s, 1 H) 7.4 (s, 1 H) 7.6 (t, J 5.9 Hz, 1 H) 8.2 (s, 1H);

8-[(1-Metilimidazol-2-il)metilamino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B82-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 3.7 (s, 3 H) 4.3 (s, 3 H) 4.6 (m, 2 H) 6.9 (s, 1 H) 7.17 (s, 1 H) 7.24 (s, 1 H) 7.43 (s, 1 H) 7.5 (m, 1 H) 8.3 (s, 1 H);

8-[(4-Aminobenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B83-X00-M00(C01)-D03]

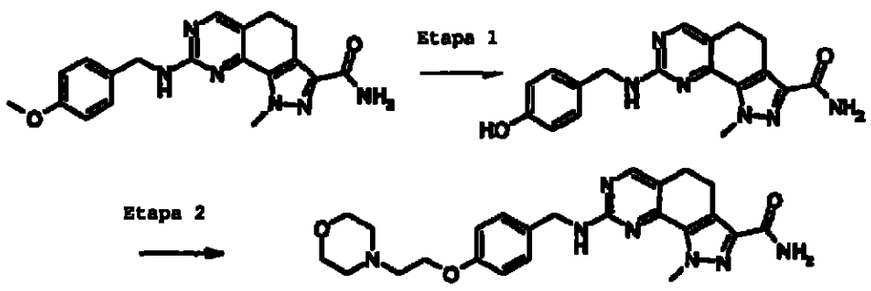
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.7 (m, 2 H) 2.9 (t, J 7.7 Hz, 2 H) 4.3 (s, 3 H) 4.4 (d, J 6.1 Hz, 2 H) 5.1 (s, 2 H) 6.5 (d, J8.4 Hz, 2 H) 7.0 (d, J8.3 Hz, 2 H) 7.2 (s, 1 H) 7.4 (m, 2 H) 8.2 (s, 1 H);

8-[(4-Fluorobenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (t, J=7.74 Hz, 2 H) 2.94 (t, J=7.56 Hz, 2 H) 4.18 (s, 3 H) 4.52 (d, J=6.22 Hz, 2 H) 7.13 (t, J=8.90 Hz, 2 H) 7.23 (s, 1 H) 7.38 (dd, J=8.66, 5.61 Hz, 2 H) 7.42 (t, 1 H) 7.71 (t, J=5.97 Hz, 1 H) 8.23 (s, 1 H).

Ejemplo 48

8-{[4-(2-morfolinoetoxi)benzil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B84-X00-M00(C01)-D03]



Etapa 1. **8-[(4-Hidroxibenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida** [B85-X00-M00(C01)-D03]

A una solución bien agitada de 8-[(4-metoxibenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida

(242 mg, 0.7 mmol) en cloroformo (30 mL) se agregó tribromuro de boro (1 M en diclorometano, 5.12 mL, 5.1 mmol) gota a gota durante un periodo de 5 minutos, a temperatura ambiente. La mezcla se calentó a reflujo durante 8 horas. Una solución de hidróxido de amonio acuoso al 10% (30 mL) se agregó gota a gota a 0°C durante un periodo de 10 minutos. Se formó un precipitado y, después de 2 horas, este se filtró y se lavó con agua y se secó a 40°C bajo vacío. Se obtuvieron 130 mg del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.8 (m, 4 H) 4.2 (s, 3 H) 4.5 (m, 2 H) 6.7 (d, J 8.65 Hz, 2 H) 7.2 (d, J 8.5 Hz, 2 H) 7.25 (s, 1 H) 7.4 (s, 1 H) 7.8 (m, 1 H) 8.2 (s, 1 H)

Etapa 2. 8-{[4-(2-morfolinoetoxi)benzil]amino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B84-X00-M00(C01)-D03]

A una solución de 8-[(4-hidroxibenzil)amino]-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida (70 mg, 0.2 mmol) en dimetilformamida anhidro (3 mL), se agregaron clorhidrato de N-morfolinoetilcloruro (47 mg, 0.3 mmol) y carbonato de potasio en polvo (45 mg, 3.3 mmol). La mezcla se calentó a reflujo durante 1 hora. La mezcla de reacción se vertió en agua con hielo (70 mL) y se extrajo con

diclorometano; los extractos orgánicos se lavaron con solución salina hasta un pH neutro, luego con agua y se secaron sobre Na_2SO_4. El crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 96: 4) para proporcionar un sólido blanco que se cristalizó a partir de metanol, proporcionando 47.0 mg del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.5 (m, 4 H) 2.7 (t, 2 H) 2.8 (m, 4 H) 3.6 (m, 4 H) 4.0 (t, 2 H) 4.2 (s, 3 H) 4.5 (m, 2 H) 6.9 (d, J 8.42 Hz, 2 H) 7.2 (s, 1 H) 7.25 (d, J 8.54 Hz, 2 H) 7.4 (s, 1 H) 7.6 (m, 1 H) 8.2 (s, 1 H).

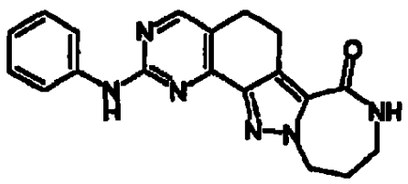
Análogamente se preparó el siguiente compuesto:

8-{[3-(2-morfolinoetoxi)-5-trifluorometil]fenilamino}-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida
[B119-X00-M00(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.47-2.56 (m, 4 H) 2.73 (t, J=7.26 Hz, 2 H) 2.85 (t, J=7.80 Hz, 2 H) 3.01 (t, J=7.80 Hz, 2 H) 3.57-3.64 (m, 4 H) 4.17 (t, J=5.49 Hz, 2 H) 4.35 (s, 3 H) 6.86 (t, J=1.83 Hz, 1 H) 7.28 (s, 1 H) 7.48 (s, 1 H) 7.61 (t, J=2.32 Hz, 1 H) 7.80 (t, J=1.46 Hz, 1 H) 8.49 (s, 1 H) 9.85 (s, 1 H).

Ejemplo 49

2-anilino-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino [1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B04-X00-M06]



Etapa 1. **7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo**



1 g (4.2 mmol) de (3-etoxi-2-oxociclohex-3-en-1-il)(oxo)acetato de etilo se disolvieron en 10 mL de etanol, 0.21 mL de hidrato de hidrazina se agregaron y la solución se agitó a reflujo durante un día. El disolvente luego se evaporó y el residuo se redisolvió con diclorometano. La capa orgánica se lavó con agua, se secó sobre Na_2SO_4 y se

concentró. El crudo se trituró con dietil éter y se filtró para dar (70 % de producto) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (t, J 6.83 Hz 3 H) 2.25-3-27 (3m, 6 H) 4.18 (q, J 6.83 Hz, 2 H) 8.45 (bs, 1 H).

Análogamente se preparó el siguiente compuesto:

4,4-dimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J=6.95 Hz, 3 H) 1.42 (s, 6 H) 1.90-2.02 (m, 2 H) 2.55-2.63 (m, 2 H) 4.33 (q, J=6.95 Hz, 2 H) 14.34 (s, 1 H).

Etapa 2. **7-oxo-1(y 2)-tritil-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo**



1.20 g (4.8 mmol) de 7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo se disolvieron en 40 mL de diclorometano y 0.76 mL de trietilamina y 1.47 g (5.3 mmol) de cloruro de trifenilmetilo se agregaron. La solución se agitó a temperatura ambiente durante 6 horas. Luego la solución se diluyó con diclorometano adicional y se lavó con agua. La capa orgánica se trató con Na_2SO_4 anhidro y se evaporó hasta secado. El producto, como una mezcla de regioisómeros, finalmente se obtuvo mediante cristalización a partir de dietil éter (80 % de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, 3 H) 1.94-2.98 (3m, 6 H) 4.25 (q, 2 H) 6.85-7.36 (2m, 15 H).

Análogamente se prepararon los siguientes compuestos:

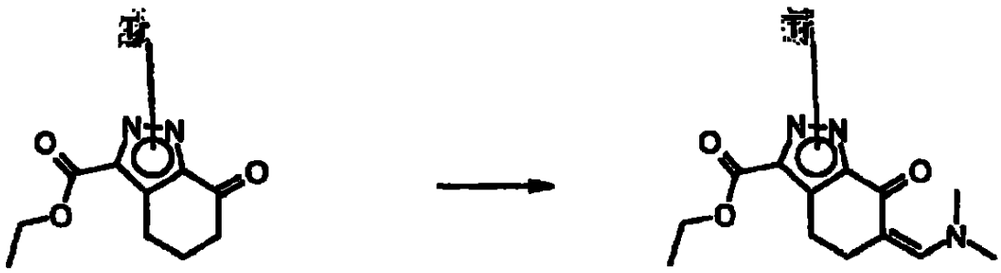
1-tritil-4,4-dimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-D6) δ ppm 1.26 (t, J=7.07 Hz, 3 H) 1.45 (s, 6 H) 1.79-1.88 (m, 2 H) 2.18-2.26 (m, 2 H) 4.27 (q, J=7.15 Hz, 2 H) 6.84-7.01 (m, 6 H) 7.14-7.33 (m, 9 H);

2-tritil-4,4-dimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (t, J=7.13 Hz, 3 H) 1.27 (s, 6 H) 1.92-1.99 (m, 2 H) 2.56-2.63 (m, 2 H) 3.44 (q, J=7.15Hz, 2H) 6.99-7.05 (m, 6 H) 7.31-7.37 (m, 9 H).

Etapa 3. -6-[(dimetilamino)metileno]-7-oxo-1(2)-tritil-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo



3.0 g (6.6 mmol) de 7-oxo-1(2)-tritil-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo se disolvieron en 20 mL de dimetilformamida y se agregaron 3.2 mL (13.2 mmol) de ditercbutilacetato de dimetilformamida. La solución se calentó a 65°C bajo agitación durante un día y luego se evaporó hasta secado. El producto se obtuvo mediante cristalización a partir de una mezcla de dietil éter/acetato de etilo (90 % de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 y 0.79 (2t, J 7.07 Hz, 3 H) 2.70-2.90 (2t, J6.71 Hz, 6 H) 2.94 y 2.99 (2m, 6 H) 4.21 (q, J7.07 Hz, 2 H) 6.90-7.30 (m, 15 H).

Análogamente se prepararon los siguientes compuestos:

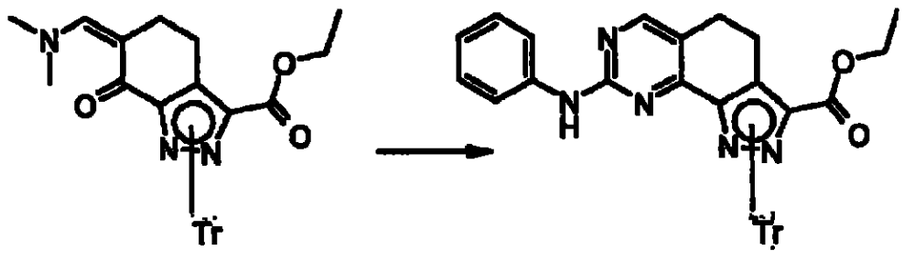
6-[(dimetilamino)metileno]-1-tritil-4,4-dimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, J=7.13 Hz, 3 H) 1.36 (s, 6 H) 2.66 (s, 2 H) 2.98 (s, 6 H) 4.25 (q, J=7.15 Hz, 2 H) 6.96 (t, 7 H) 7.15-7.29 (m, 9 H);

6-[(dimetilamino)metileno]-2-tritilo-4,4-dimetil-7-oxo-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.90 (t, J=7.19 Hz, 3 H) 1.19 (s, 6 H) 2.78 (s, 2 H) 3.11 (s, 6 H) 3.42 (q, J=7.23 Hz, 2 H) 6.97-7.09 (m, 6 H) 7.30-7.37 (m, 9 H) 7.48 (s, 1 H).

Etapa 4. **8-anilino-1(y 2)-tritil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo**



A una solución de 636 mg de 6-[(dimetilamino) metilene]-7-oxo-1(2)-tritil-4,5,6,7-tetrahidro-1H-indazol-3-carboxilato de etilo (1.18 mmol) y 440 mg (1.18 mmol) de carbonato de fenilguanidina en 100 mL de etanol absoluto, se agregaron 0.5 mL de diazabicicloundeceno. La mezcla se agitó a reflujo durante 48 horas y luego el disolvente se evaporó bajo presión reducida. El residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4 y se purificó mediante cromatografía sobre columna de gel de sílice (eluente ciclohexano/acetato de etilo 8/2) para dar 240 mg del compuesto del título (35% de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.81 (t, J 7.20 Hz, 3 H) 2.80-2.95 (m, 4 H) 3.58 (q, J7.20 Hz, 2 H) 6.85-7.80 (5m, 20H) 8.38 (bs, 1 H) 9.49 (bs, 1 H).

De acuerdo con el mismo método pero empleando los derivados de guanidina adecuados, se prepararon los siguientes compuestos:

8-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)fenil]amino}-1(y 2)-tritil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

8-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-1(y 2)-tritil-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

8-{[4-(4-metilpiperazin-1-il)fenil]amino}-1(y 2)-tritil-4,5-dihidro-2H-pirazolo[4,3-h] quinazolina-3-carboxilato de etilo

8-amino-1(y 2)-tritil-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

8-[4-(4-metil-piperazin-1-il)-fenilamino]-1-tritil-4,4 dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, J 7.20 Hz, 3 H) 1.31 (s, 6 H) 2.20 (s, 3 H) 2.43 (m, 4 H) 2.56 (m, 2 H) 2.99 (m, 4 H) 4.24 (q, J 7.20 Hz, 2 H) 6.61 (d, J=8.79 Hz, 2 H) 6.92-7.37 (m, 17 H) 8.07 (bs, 1 H);

8-[4-(4-metil-piperazin-1-il)-fenilamino]-2-tritil-4,4 dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, J7.20 Hz, 3 H) 1.17 (s, 6 H) 2.21 (s, 3 H) 2.46 (m, 4 H) 2.71 (m, 2 H) 3.04 (m, 4

H) 3.40 (q, J 7.20 Hz, 2 H) 6.80 (d, J=8.79 Hz, 2 H) 6.96-7.43 (m, 15 H) 7.60 (d, J=8.79 Hz, 2 H) 8.31 (bs, 1 H) 9.31 (bs, 1 H);

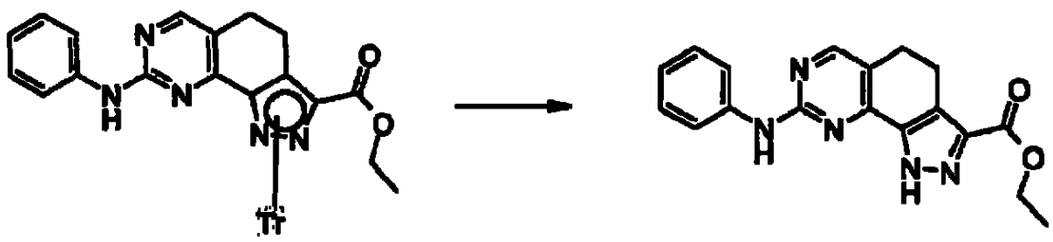
8-anilino-1(y 2)-tritil-4,4 dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;
8-amino-1-tritil-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (t, J=7.13 Hz, 3 H) 1.31 (s, 6 H) 2.52 (s, 2 H) 4.27 (q, J=7.07 Hz, 2 H) 5.20 (s, 2 H) 7.03-7.09 (m, 6 H) 7.16-7.34 (m, 9 H) 7.93 (s, 1 H);

8-amino-2-tritil-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (t, J=7.13 Hz, 3 H) 1.16 (s, 6 H) 2.63 (s, 2 H) 3.46 (q, J=7.07 Hz, 2 H) 6.47 (s, 2 H) 7.09-7.16 (m, 6 H) 7.24-7.41 (m, 9 H) 8.14 (s, 1 H).

Etapa 5. **8-anilino-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B04-X00-M00(C00)-D01]**



1.50 g (2.6 mmol) de 8-anilino-1(2)-tritil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo se disolvieron en 50 mL de diclorometano y se agregaron 5 mL de ácido trifluoroacético. La solución se agitó durante la noche y el disolvente se removió en vacío. El residuo se redisolvió en diclorometano y se lavó con una solución saturada de $NaHCO_3$. La capa orgánica luego se secó sobre Na_2SO_4 y el disolvente se evaporó hasta secado. Mediante cristalización a partir de diisopropil éter se ontuvieron 0.70 mg del compuesto del título (80 % de producto).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, 3 H, J 7.07 Hz) 3.05-3.28 (2m, 4 H) 4.18 (q, 2 H, J 7.07 Hz) 6.83-7.63 (3m, 5 H) 8.31 (bs, 1 H) 9.10 (m, 2 H).

De acuerdo con el mismo método se prepararon los siguientes compuestos:

8-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B12-X00-M00(C00)-D01]

8-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B13-X00-M00(C00)-D01]

8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2 H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B10-X00-M00(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (t, J7.20 Hz, 3H) 2.30 (s, 3 H) 2.50-2.60 (m, 4 H) 2.86 (m, 2 H) 2.99 (m, 2 H) 3.10 (m, 4 H) 4.33 (q, J 7.20 Hz, 2 H) 6.90 (d, J=8.90 Hz, 2 H) 7.71 (d, J=8.90 Hz, 2 H) 8.34 (s, 1H) 9.27 (bs, 1H) 14.22 (bs, 1 H)

8-amino-4,5-dihidro-1H-pirazolo[4,3-h}quinazolina-3-carboxilato de etilo [B00-X00-M00(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, 3 H, J 7.2 Hz) 2.78 (m, 2 H) 2.96 (m, 2 H) 4.31 (q, 2 H, J 7.2 Hz) 6.64 (m, 2 H) 8.19 (bs, 1 H);

8-[4-(4-metil-piperazin-1-il)-fenilamino]-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolinie-3-carboxilato de etilo [B10-X00-M03(C00)-D01]

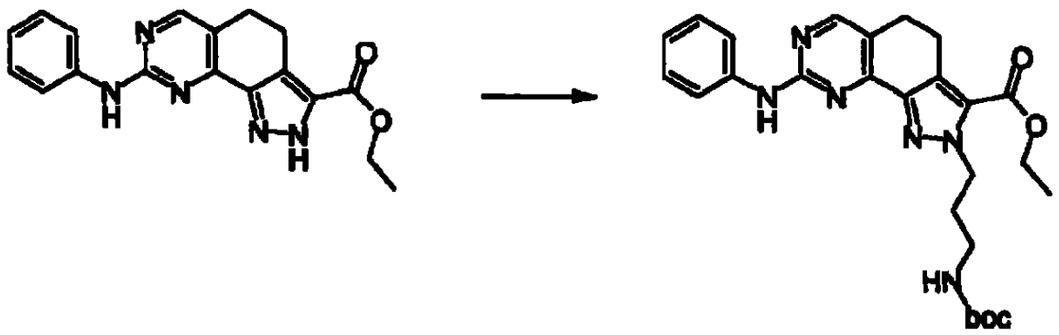
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (t J 7.20 Hz, 3 H) 1.33 (s, 6 H) 2.22 (s, 3 H) 2.40-2.50 (m, 4 H) 2.73 (m, 2 H) 3.07 (m, 4 H) 4.35 (q, J 7.20 Hz, 2 H) 6.91 (d, J=9.02 Hz, 2 H) 7.70 (d, J=9.02 Hz, 2 H) 8.33 (bs, 1 H) 9.30 (bs, 1 H) 14.13 (bs, 1 H);

8-amino-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-H]quinazolina-3-carboxilato de etilo [B00-X00-M03(C00)-D01]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 9 H) 2.66 (s, 2 H) 4.22-4.42 (m, 2 H) 6.36 (d, 2 H) 8.19 (d, 1 H) 14.11 (d, 1 H);

8-anilino-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo [B04-X00-M03(C00)-D01].

Etapa 6. **8-anilino-2-{3-[(terc-butoxicarbonil)amino]propil}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo**



500 mg de 8-anilino-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo (1.5 mmol) se disolvieron en 10 mL de dimetilformamida seca y se agregaron 1.63 mL de terc-butóxido de litio al 1M en tetrahidrofurano a la solución enfriada. Después de 30 minutos bajo agitación a 0°C una solución de 432 mg de bromuro de terc-butoxicarbonilaminopropilo en 8 mL de tetrahidrofurano seco se agregaron gota a gota. Después de una noche a temperatura ambiente la mezcla se vertió en una solución de NaH_2PO_4 y se extrajo con diclorometano. La capa orgánica luego se secó sobre Na_2SO_4 y el disolvente se evaporó, dando un aceite que se trató de acuerdo con la siguiente Etapa 7, sin ninguna purificación adicional.

Análogamente se pueden preparar los siguientes compuestos:

2-{3-[(terc-butoxicarbonil)amino]propil}-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

2-{3-[(terc-butoxicarbonil)amino]propil}-8-{[4-(4-metilpiperazin-1-il)-3-(trifluorometilfenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

2-{3-[(terc-butoxicarbonil)amino]propil}-8-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

8-amino-2-{3-[(terc-butoxicarbonil)amino]propil}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

8-amino-2-{3-[(terc-butoxicarbonil)amino]propil}-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

8-[4-(4-metil-piperazin-1-il)-fenilamino]-2-{3-[(terc-butoxicarbonil)amino]propil}-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

8-anilino-2-{3-[(terc-butoxicarbonil)amino]propil}-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo.

Siguiendo el método anterior, pero empleando bromuro de terc-butoxicarbonilaminoetilo, se prepararon los siguientes compuestos:

8-anilino-2-{2-[(terc-butoxicarbonil)amino]etil}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

2-{2-[(terc-butoxicarbonil)amino]etil}-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

2-{2-[(terc-butoxicarbonil)amino]etil}-8-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

2-{2-[(terc-butoxicarbonil)amino]etil}-8-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

8-amino-2-{2-[(terc-butoxicarbonil)amino]etil}-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

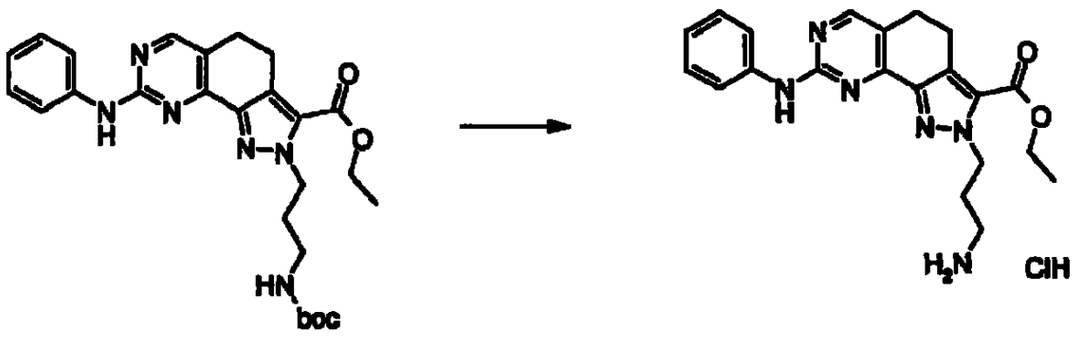
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 9H) 1.36 (t, 3 H, J 7.2 Hz) 2.74 (m, 2 H) 2.94 (m, 2 H) 3.34 (m, 2 H) 4.33 (q, 2 H, J 7.2 Hz) 4.57 (t, 2 H) 6.50 (m, 2 H) 6.87 (t, 1 H) 8.15 (bs, 1 H);

8-amino-2-{2-[(terc-butoxicarbonil)amino]etil}-4,4-dimetil-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

8-[4-(4-metil-piperazin-1-il)-fenilamino]-2-{2-[(terc-butoxicarbonil)amino]etil}-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo;

8-anilino-2-{2-[(terc-butoxicarbonil)amino]etil}-4,4-dimetil-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo.

Etapa 7. **Clorhidrato de 2-(3-aminopropil)-8-anilino-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo** [B04-X00-M04(C13)-D01]



El crudo de la Etapa 6 anterior se disolvió en 20 mL de dioxano y se agregaron 8 mL de HCl al 37%. Después de 6 horas bajo agitación a temperatura ambiente el disolvente se removió en vacío, y el residuo se trituró con etanol y el producto se recolectó mediante filtración (80 % de producto).

Al trabajar de acuerdo con el método anterior, se prepararon los siguientes compuestos:

B04-X00-M04(C12)-D01

B00-X00-M04(C12)-D01

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.37 (t, 3 H, J 7.2 Hz) 2.85 (m, 2 H) 3.02 (m, 2 H) 3.50 (m, 2 H) 4.37 (q. 2 H, J 7.2 Hz) 4.84 (t, 2 H) 7.47 (m, 1 H) 8.08 (m, 3 H) 8.29 (s, 1 H);

B12-X00-M04(C12)-D01

B13-X00-M04(C12)-D01

B10-X00-M04(C12)-D01

B12-X00-M04(C13)-D01

B13-X00-M04(C13)-D01

B10-X00-M04(C13)-D01

Clorhidrato de 8-amino-2-(3-aminopropil)-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B00-X00-M04(C13)-D01;

Clorhidrato de 8-amino-2-(3-aminopropil)-4, 4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B00-X00-M09(C13)-D01;

Clorhidrato de 2-(3-aminopropil)-8-[4-(4-metil-piperazin-1-il)-fenilamino]-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B10-X00-M09(C13)-D01;

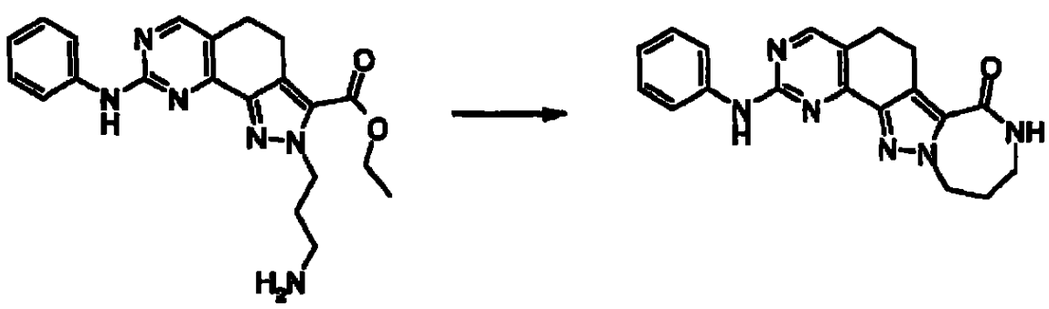
Clorhidrato 8-anilino-2-(3-aminopropil)-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B04-X00-M09(C13)-D01;

Clorhidrato de 8-amino-2-(3-aminoetil)-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B00-X00-M09 (C12)-D01;

Clorhidrato de 2-(3-aminoetil)-8-[4-(4-metil-piperazin-1-il)-fenilamino]-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B10-X00-M09(C12)-D01;

Clorhidrato de 8-anilino-2-(3-aminoetil)-4,4-dimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo B04-X00-M09 (C12)-D01.

Etapa 8. **2-anilino-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino [1',2':1,5] pirazolo[4,3-h]quinazolin-7-ona** [B04-X00-M06]



185 mg (0.43 mmol) de clorhidrato de 2-(3-aminopropil)-8-anilino-4,5-dihidro-2H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo se disolvieron en 10 mL de metanol y se agregaron 400 mg de carbonato de cesio. Después de 3 horas bajo agitación a temperatura ambiente el disolvente se removió a presión reducida. Luego se agregó agua al residuo y

el sólido se recolectó mediante filtración y se lavó con agua y acetona para dar 100 mg (70% de producto) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (ddd, J 13.02, 6.65, 6.55 Hz, 2 H) 2.88 (m, 4 H) 3.21 (q, J5.89 Hz, 2 H) 4.50 (t, J6.77 Hz, 2 H) 6.93 (t, J7.32 Hz, 1 H) 7.28 (dd, J 8.29, 7.56 Hz, 2 H) 7.85 (d, J7.68 Hz, 2 H) 8.27 (t, J 5.18 Hz, 1 H) 8.38 (s, 1 H) 9.62 (s, 1 H).

Al trabajar de acuerdo con este método se prepararon los siguientes compuestos:

2-anilino-5,6,9,10-tetrahidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B04-X00-M05]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 (m, 4 H) 3.65 (m, 2 H) 4.41 (m, 2 H) 6.93 (m, 1 H) 7.28 (m, 2 H) 7.85 (m, 2 H) 8.26 (m, 1 H) 8.39 (s, 1 H) 9.61 (s, 1 H);

2-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)fenil]amino}-5,6,9,10-tetrahidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B12-X00-M05]

2-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-5,6,9,10-tetrahidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B13-X00-M05]

2-{[4-(4-metilpiperazin-1-il)fenil]amino}-5-,6,9,10-tetrahidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B10-X00-M05]

2-amino-5,6,9,10-tetrahidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B00-X00-M05]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (t, J=7.56 Hz, 2 H) 2.88-2.98 (m, 2 H) 3.60-3.68 (m, 2 H) 4.29-4.42 (m, 2 H) 6.48 (s, 2 H) 8.15 (s, 1 H) 8.21-8.32 (m, 1 H);

2-amino-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B00-X00-M06]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (ddd, J 13.02, 6.65, 6.55 Hz, 2 H) 2.74 (m, 2 H) 2.92 (m, 2 H) 3.21 (q, J5.89 Hz, 2 H) 4.50 (t, J6.77 Hz, 2 H) 6.48 (m, 2 H) 8.17 (s, 1 H) 8.23 (m, 1 H);

2-{[4-(4-metilpiperazin-1-il)-3-(trifluorometil)fenil]amino}-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B12-X00-M06]

2-{[3-cloro-4-(4-metilpiperazin-1-il)fenil]amino}-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B13-X00-M06]

2-{[4-(4-metilpiperazin-1-il)fenil]amino}-5,6,8,9,10,11-hexahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B10-X00-M06]

2-amino-6,6-dimetil-5,9,10-trihidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B00-X00-M07];

2-anilino-6,6-dimetil-5,9,10-trihidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B04-X00-M07];

2-[4-(4-metil-piperazin-1-il)-fenilamino]-6,6-dimetil-5,9,10-trihidropirazino[1',2':1,5]pirazolo[4,3-h]quinazolin-7(8H)-ona [B10-X00-M07]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.92 (m, 2 H) 3.07 (m, 4 H) 3.65 (m, 2 H) 4.41 (m, 2 H) 6.91 (d, J=9.02 Hz, 2 H) 7.53 (d, J=9.02 Hz, 2 H) 8.23 (m, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H);

2-amino-6,6-dimetil-5,8,9,10,11-pentahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B00-X00-M08];

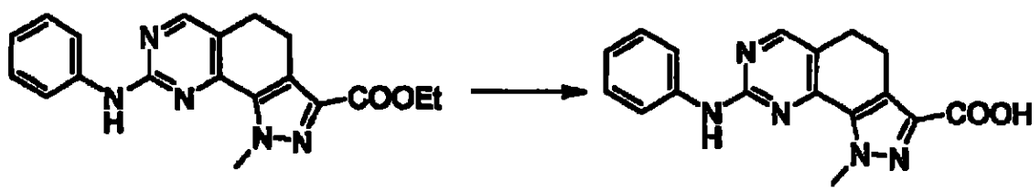
2-anilino-6,6-dimetil-5,8,9,10,11-pentahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B04-X00-M08];

2-[4-(4-metil-piperazin-1-il)-fenilamino]-6,6-dimetil-5,8,9,10,11-pentahidro-7H-[1,4]diazepino[1',2':1,5]pirazolo[4,3-h]quinazolin-7-ona [B10-X00-M08]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.18 (ddd, J 13.02, 6.65, 6.55 Hz, 2 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.92 (m, 2 H) 3.07 (m, 4 H) 3.21 (q, J5.89 Hz, 2 H) 4.50 (t, J 6.77 Hz, 2 H) 6.91 (d, J=9.02 Hz, 2 H) 7.53 (d, J=9.02 Hz, 2 H) 8.27 (m, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H).

Ejemplo 50

Ácido 8-anilino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B04-X00-M00(C01)-D02]



0.63 g (1.80 mmol) de 8-anilino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo se disolvieron en 100 mL de una mezcla de tetrahidrofurano/metanol/agua 8/1/1 y se agregaron 0.19 g (4,53 mmol) de hidrato de hidróxido de litio. La solución se agitó a 60°C durante 1.5 horas. La mezcla luego se enfrió a

temperatura ambiente y se agregó HCl al 1N hasta pH neutro. Se agregó agua y el precipitado resultante se recolectó mediante filtración (87% de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (t, J7.74 Hz, 2 H) 2.99 (m, 2 H) 4.36 (s, 3 H) 6.98 (tt, J 7.35, 1.07 Hz, 1 H) 7.31 (dd, J 8.47, 7.50 Hz, 2 H) 7.72 (dd, J 8.60, 0.91 Hz, 2 H) 8.42 (s, 1 H) 9.52 (s, 1 H) 12.68 (s, 1 H)

Al trabajar de acuerdo con el mismo procedimiento se prepararon los siguientes compuestos:

B00-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.48 y 3.64 (2t, J7.25 Hz, 4 H) 3.84 (s, 3 H) 8.04 (bs, 2 H) 8.46 (bs, 1 H);

B09-X00-M00(C03)-D02

^{1}H NMR (400 MHz, DMSO-d_6 Hz) 6.49 (m, 1 H) 7.07 (m, 2 H) 7.94 (bs, 1 H) 8.30 (s, 1 H) 9.35 (bs, 1 H);

B09-X00-M04(C03)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 (s, 9H) 1.62 (m, 2 H) 2.26 (s, 3 H) 2.52 (m, 4 H) 3.13 (m, 4 H) 4.86 (m, 2 H) 6.58 (m, 1 H) 7.13 (m, 1 H) 7.20 (m, 1 H) 8.41 (s, 1 H) 9.20 (bs, 1 H);

B10-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (s, 3 H) 2.74 (m, 2 H) 2.95 (m, 2 H) 4.30 (s, 3 H) 6.93 (m, 2 H) 7.52 (m, 2 H) 8.33 (s, 1 H) 9.28 (bs, 1 H);

B103-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 (m, 4 H) 2.83 (m, 5 H) 2.97 (t, 2 H) 4.33 (s, 3 H) 7.02 (m, 2 H) 7.61 (m, 2 H) 8.38 (s, 1 H) 9.39 (s, 1 H);

B09-X00-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (m, 5 H) 2.93 (t, 2 H) 3.09 (m, 4 H) 3.71 (m, 4 H) 4.32 (s, 3 H) 6.64 (m, 1 H) 7.17 (m, 1 H) 7.29 (m, 2 H) 8.38 (s, 1 H) 9.42 (s, 1 H) 10.33 (s, 1 H);

B04-X04-M00(C01)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.89 (t, 2 H) 2.97 (t, 2 H) 3.70 (s, 3 H) 7.51 (m, 3 H) 7.67 (m, 2 H) 8.56 (s, 1 H) 12.81 (bs, 1 H);

B05-X06-M00(C01)-D02

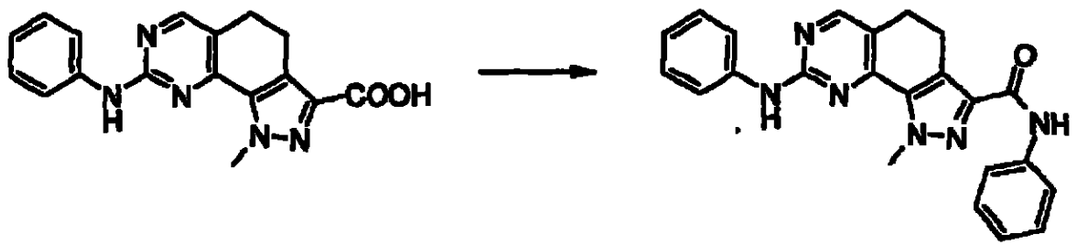
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 (t, 2 H) 2.97 (t, 2 H) 4.23 (s, 2 H) 4.26 (s, 3 H) 7.23 (m, 1 H) 7.32 (m, 2 Et) 7.36 (m, 2 H) 8.65 (s, 1 H) 12.82 (bs, 1 H);

B10-X00-M04(C15)-D02

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.60 (m, 5 H) 2.89 (m, 2 H) 3.04 (m, 4 H) 3.33 (m, 4 H) 6.31 (s, 2 H) 6.78 (d, 2 H) 7.39 (m, 3 H) 7.47 (m, 2 H) 7.63 (m, 2 H) 7.67 (s, 1 H) 8.42 (s, 1 H) 9.33 (s, 1 H) 13.55 (s, 1H).

Ejemplo 51

8-anilino-1-metil-N-fenil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B04-X00-M00(C01)-D20]



45 mg (0.14 mmol) de ácido 8-anilino-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico se disolvieron en 7 mL de dimetilformamida y 145.6 mg (0.28 mmol) de hexafluorofosfato de (benzotriazol-1-iloxi) tripirrolidinofosfonio (PyBOP); 0.12 mL (0.70 mmol) de amina

de N,N-diisopropil-N-etilo y 0.08 mL (0.70 mmol) de anilina se agregaron. Después de 6 horas el disolvente se removió, el residuo se redisolvió con diclorometano y se lavó con agua. La capa orgánica se secó sobre Na_2SO_4 y se evaporó hasta secado. El producto se cristalizó a partir de metanol (60% de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.88 (m, 2 H) 3.07 (m, 2 H) 4.43 (s, 3 H,) 6.97-7.85 (6m, 10H) 8.45 (s, 1 en 9.55 (s, 1 H) 10.09 (s, 1 H).

Al trabajar análogamente se prepararon los siguientes compuestos:

Tabla XIII

B04-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.72 (d, *J*=4.76 Hz, 3 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.97 (t, *J*=7.68 Hz, 2 H) 4.31 (s, 3 H) 6.94 (t, *J*=7.38 Hz, 1 H) 7.21 - 7.32 (m, 2 H) 7.68 (d, *J*=7.56 Hz, 2 H) 8.06 (q, *J*=4.35 Hz, 1 H) 8.38 (s, 1 H) 9.48 (s, 1 H)
B04-X00-M00(C01)-D08	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (m, 4 H) 2.83 (m, 2 H) 2.94 (m, 2 H) 3.49 (t, *J* 6.77 Hz, 2 H) 3.83 (t, *J* 6.58 Hz, 2 H) 4.34 (s, 3 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (dd, *J* 8.29, 7.56 Hz, 2 H) 7.73 (d, *J* 7.44 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B04-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 (m, 2 H) 3.01 (m, 2 H) 4.36 (s, 3 H) 4.43 (d, *J* 6.34 Hz, 2 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (m, 7 H) 7.72 (d, *J* 7.5 Hz, 2 H) 8.42 (s, 1 H) 8.71 (t, *J* 6.4 Hz, 1 H) 9.52 (s, 1 H)

B04-X00-M00(C01)-D10	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65-3.5 (m, 15 H) 4.35 (s, 3 H) 6.98 (t, *J* 7.4 Hz, 1 H) 7.32 (dd, *J* 8.29, 7.56 Hz, 2 H) H) 7.73 (d, *J* 7.5 Hz, 2 H) 8.44 (s, 1 H) 9.55 (s, 1 H)
B04-X00-M00(C01)-D11	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.88 (d, *J* 6.71 Hz, 6 H) 1.86 (m, 1 H) 2.83 (dd, *J* 8.05, 7.19 Hz, 2 H) 3.00 (t, *J* 7.74 Hz, 2 H) 3.07 (t, *J* 6.58 Hz, 2 H) 4.36 (s, 3 H) 6.97 (tt, *J* 7.32, 1.10 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.50 Hz, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.09 (t, *J* 6.16 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D12	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (m, 2 H) 3.01 (m, 2 H) 3.28 (s, 3 H) 3.43 (m, 4 H) 4.36 (s, 3 H) 6.98 (m, 1 H) 7.31 (dd, *J* 8.41, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 7.99 (t, *J* 5.49 Hz, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D13	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.16 (m, 6 H) 1.83 (m, 2 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 2.9-3.5 (m, 8 H) 4.36 (s, 3 H) 6.97 (m, 1 H) 7.31 (m, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.09 (t, *J* 6.16 Hz, 1 H) 8.43 (s, 1 H) 9.53 (s, 1 H)
B04-X00-M00(C01)-D14	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54 (m, 4 H) 1.70 (m, 2 H) 1.85 (m, 2 H) 2.83 (m, 2 H) 3.0 (m, 2 H) 4.21 (m, 1 H) 4.35 (s, 3 H) 6.97 (t, *J* 7.32 Hz, 1 H) 7.31 (dd, *J* 8.29, 7.56 Hz, 2 H) 7.73 (d, *J* 7.44 Hz, 2 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B04-X00-M00(C01)-D15	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 (s, 3 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 3.06 (m, 8 H) 4.42 (s, 3 H) 6.75 (m, 1 H) 6.99 (t, *J* 7.32 Hz, 1 H) 7.20 (t, *J* 8.05 Hz, 1 H) 7.32 (m, 3 H) 7.55 (bs, 1 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.45(s, 1 H) 9.55 (s, 1 H) 9.91 (s, 1 H)
B04-X00-M00(C01)-D16	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (m, 2 H) 3.01 (m, 2 H) 4.35 (s, 3 H) 4.43 (d, *J* 6.10 Hz, 2 H) 6.25 (dd, *J* 3.17, 0.85 Hz, 1 H) 6.40 (dd, *J* 3.17, 1.83 Hz, 1 H) 6.97 (m, 1 H) 7.31 (dd, *J* 8.54, 7.44 Hz, 2 H) 7.57 (dd, *J* 1.83, 0.85 Hz, 1 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.42 (s, 1 H) 8.54 (t, *J* 6.04 Hz, 1 H) 9.52 (s, 1 H)
B04-X00-M00(C01)-D17	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.7 (m, 2 H) 2.83 (m, 2 H) 3.01 (m, 2 H) 3.2-3.7 (m, 12 H) 4.35 (s, 3 H) 6.98 (m, 1 H) 7.32 (dd, *J* 8.54, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.38 (m, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B00-X00-M00(C21)-D04]	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (d, *J*=10.73 Hz, 2 H) 2.11 - 2.31 (m, 4 H) 2.70 (t, *J*=7.93 Hz, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.86 - 3.02 (m, *J*=7.56, 7.56 Hz, 4 H) 3.55 (s, 2 H) 5.50 - 5.62 (m, 1 H) 6.51 (s, 2 H) 7.19 - 7.39 (m, 5 H) 7.93 - 8.04 (m, 1 H) 8.17 (s, 1 H)
B00-X00-M00(C01)-D18	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 3.03

	(m, 2 H) 4.40 (s, 3 H) 6.61 (bs, 2 H) 7.18 (m, 1 H) 7.87 (m, 1 H) 8.18 (m, 1 H) 8.22 (m, 1 H) 8.37 (m, 1 H) 9.46 (s, 1 H).
B04-X00-M00(C01)-D27	
B04-X00-M04(C01)-D27	
B04-X00-M00(C21)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 (d, *J*=9.76 Hz, 2 H) 2.00 - 2.10 (m, 2 H) 2.13 - 2.28 (m, 2 H) 2.81 (t, *J*=7.44 Hz, 2 H) 2.88 (d, *J*=11.22 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.51 (s, 2 H) 4.42 - 4.50 (m, *J*=6.46 Hz, 2 H) 5.49 - 5.62 (m, 1 H) 6.99 - 7.40 (m, 13 H) 7.61 (d, *J*=8.66 Hz, 2 H) 8.42 (s, 1 H) 8.68 (t, *J*=6.16 Hz, 1 H) 9.44 (s, 1 H)
B04-X00-M00(C01)-D19	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 4 H) 3.01 (m, 2 H) 3.49 (m, 2 H) 4.35 (s, 3 H) 6.97 (m, 1 H) 7.31 (m, 7 H) 7.72 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.18 (m, 1 H) 8.42 (s, 1 H) 9.52 (s, 1 H)
B10-X00-M00(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (d, *J*=4.76 Hz, 3 H) 2.81 (t, *J*=7.68 Hz, 2 H) 2.85 (d, *J*=4.39 Hz, 3 H) 2.94 - 3.07 (m, 4 H) 3.11 - 3.25 (m, 2 H) 3.51 (d, *J*=11.83 Hz, 2 H) 3.73 (d, *J*=13.66 Hz, 2 H) 4.33 (s, 3 H) 6.99 (d, *J*=9.15 Hz, 2 H) 7.60 (d, *J*=9.02 Hz, 2 H) 8.08 (q, *J*=4.67 Hz, 1 H) 8.37 (s, 1 H) 9.40 (s, 1 H) 10.36 (s, 1 H)
B10-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.29 (s, 3 H) 2.55 (m, 4 H) 2.80 (m, 2 H) 2.99 (m, 2 H) 3.10 (m, 2 H) 4.34 (s, 3 H) 4.44 (d, *J* 6.34 Hz, 2 H) 6.92 (d, *J* 9.02 Hz, 2 H) 7.25 (m, 1 H) 7.32 (m, 4 H) 7.72 (d, *J* 7.5 Hz, 2 H) 8.35 (s, 1 H) 8.69 (t, *J* 6.4 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 3.34 (m, 4 H), 4.34 (s, 3 H), 4.40 (d, 2 H), 6.93 (d, 2 H), 7.15 (t, 2 H), 7.37 (t, 2 H), 7.53 (d, 2 H), 8.35 (s, 1 H), 8.74 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D22	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 3.34 (m, 4 H), 3.74, (s, 3 H), 4.33 (d+s, 5 H), 6.90 (t, 4 H), 7.25 (d, 2 H), 7.53 (d, 2 H), 8.35 (s, 1 H), 8.60 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D23	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H), 2.52 (m, 4 H), 2.80 (t, 2 H), 2.99 (t, 2 H), 3.09 (bs, 4 H), 4.35 (s, 3 H), 4.50 (d, 2 H), 6.93 (d, 2 H), 7.55 (m, 4 H), 7.69 (d, 2 H), 8.35 (s, 1 H), 8.87 (t, 1 H), 9.26 (s, 1 H).
B10-X00-M00(C01)-D24	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H), 2.24 (s, 3 H), 2.47 (m, 4 H), 2.78 (t, 2 H), 2.96 (t, 2 H), 3.08 (m, 4 H), 4.35 (s, 3 H), 5.15 (m, 1 H), 6.91 (d, 2 H), 7.24 (m, 1 H), 7.33 (t, 2 H), 7.42 (m, 2 H), 7.53 (d, 2 H), 8.34 (s, 1 H), 8.43 (d, 1 H), 9.25 (s, 1 H).
B10-X00-M00(C19)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 2.24

	(s, 3 H) 2.48 (m, 4 H) 3.12 (m, 4 H) 5.44 (m, 1 H) 6.95 (m, 2 H) 7.38 (m, 2 H) 7.94 (s, 1 H) 8.34 (s, 1 H) 9.12 (s, 1 H).
B10-X00-M00(C01)-D40	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.80 (t, 2 H) 2.99 (t, 3 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 4.43 (d, 2 H) 6.93 (d, 2 H) 7.07 (m, 1 H) 7.14 (m, 1 H) 7.18 (m, 1 H) 7.37 (m, 1 H) 7.53 (d, 2 H) 8.35 (m, 1 H) 8.79 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D16	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 (m, 15 H) 4.33 (s, 3 H) 4.43 (d, *J*=5.97 Hz, 2 H) 6.25 (dd, *J*=3.17, 0.85 Hz, 1 H) 6.40 (dd, *J*=3.23, 1.89 Hz, 1 H) 6.94 (d, *J*=9.02 Hz, 2 H) 7.56 (d, *J*=9.02 Hz, 2 H) 7.57 (dd, *J*=1.83, 0.85 Hz, 1 H) 8.36 (s, 1 H) 8.52 (t, *J*=6.16 Hz, 1 H) 9.29 (s, 1 H)
B10-X00-M00(C01)-D76	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 12 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.59 (m, 4 H) 4.33 (s, 3 H) 6.92 (d, 2 H) 7.52 (d, 2 H) 7.99 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D47	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (s, 3 H) 2.64 (m, 4 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.13 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.54 (d, 2 H) 8.34 (s, 1 H) 8.42 (d, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D61	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (d, 3 H) 2.27 (s, 3 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.52 (d, 2 H) 8.34 (s, 1 H) 8.42 (d, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D50	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.60 (s, 3 H) 4.32 (s, 3 H) 4.39 (d, 2 H) 5.89 (m, 1 H) 5.97 (m, 1 H) 6.64 (m, 1 H) 6.92 (d, 2 H) 7.52 (d, 2 H) 8.26 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.49 (m, 4 H) 2.82 (t, 2 H) 3.01 (t, 2 H) 3.10 (m, 4 H) 4.38 (s, 3 H) 4.46 (d, 2 H) 6.94 (d, 2 H) 7.33 (d, 2 H) 7.55 (d, 2 H) 8.37 (s, 1 H) 8.52 (d, 2 H) 8.88 (t, 1 H) 9.29 (s, 1 H)
B10-X00-M00(C01)-D45	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.09 (m, 4 H) 4.34 (s, 3 H) 4.44 (d, 2 H) 6.93 (d, 2 H) 7.38 (m, 1 H) 7.53 (d, 2 H) 7.72 (m, 1 H) 8.35 (s, 1 H) 8.46 (m, 1 H) 8.55 (m, 1 H) 8.83 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (m, 3 H) 2.53 (m, 4 H) 2.78 (m, 2 H) 2.94 (m, 2 H) 3.10 (m, 4 H) 3.74 (m, 2 H) 4.37 (m, 3 H) 5.00 (t, 1 H) 5.03 (m, 1 H) 6.92 (m, 2 H) 7.25 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.54 (m, 2 H) 8.27 (d, 1 H) 8.34 (m, 1 H) 9.26 (m, 1 H)

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B10-X00-M00(C01)-D60	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, *J*=7.74 Hz, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 3.74 (m, 2 H) 4.37 (s, 3 H) 5.01 (m, 2 H) 6.92 (d, 2 H) 7.30 (m, 5 H) 7.53 (d, 2 H) 8.27 (d, *J*=8.29 Hz, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D42	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (s, 2 H) 3.09 (m, 4 H) 4.34 (s, 3 H) 4.39 (d, 2 H) 6.93 (d, 2 H) 7.18 (m, 1 H) 7.37 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.81 (t, 1 H) 9.26 (m, 1 H)
B10-X00-M00(C01)-D41	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J*=7.32 Hz, 3 H) 1.87 (m, 2 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.77 (m, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 4.88 (td, *J*=8.75, 6.40 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.23 (m, 1 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.42 (m, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.78 Hz, 2 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D54	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.52 (m, 10 H) 2.78 (t, 2 H) 2.95 (m, 4 H) 3.08 (m, 4 H) 3.59 (m, 4 H) 4.37 (s, 3 H) 5.16 (m, 1 H) 6.92 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, 2 H) 8.34 (s, 1 H) 8.40 (d, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D67	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H) 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 3.66 (s, 3 H) 4.30 (d, *J*=5.97 Hz, 2 H) 4.32 (s, 3 H) 5.94 (s, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.23 (t, *J*=5.97 Hz, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D49	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 3.00 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 4.33 (s, 3 H) 4.58 (d, *J*=6.22 Hz, 2 H) 6.91 (d, *J*=9.02 Hz, 2 H) 6.96 (dd, *J*=5.06, 3.48 Hz, 1 H) 7.01 (dd, *J*=3.41, 1.10 Hz, 1 H) 7.37 (dd, *J*=5.06, 1.28 Hz, 1 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.74 (t, *J*=6.22 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D68	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (t, *J*=7.26 Hz, 3 H) 1.86 (m, 2 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.78 (m, 2 H) 2.95 (m, 2 H) 3.08 (m, 4 H) 4.35 (s, 3 H) 4.88 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.78 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D64	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.83 (m, 4 H) 2.90 (m, 3 H) 3.09 (m, 4 H) 3.18 (s, 3 H) 4.30 (d, *J*=17.68 Hz, 6 H) 4.69 (s, 2 H) 4.97 (s, 2 H) 6.91 (m, *J*=9.02 Hz, 2 H) 7.29 (m, 5 H) 7.52 (m, 2 H) 8.36 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D53	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m,

	4 H) 4.37 (s, 3 H) 5.13 (m, 1 H) 6.93 (d, 2 H) 7.41 (d, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.51 (m, 2 H) 8.66 (d, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72 (s, 6 H) 2.26 (s, 3 H) 2.50 (m, 4 H) 2.79 (t, 2 H) 2.92 (t, 2 H) 3.10 (m, 4 H) 4.38 (s, 3 H) 6.94 (d, 2 H) 7.22 (m, 1 H) 7.34 (m, 2 H) 7.43 (m, 2 H) 7.54 (d, 2 H) 7.81 (s, 1 H) 8.36 (s, 1 H) 9.28 (s, 1 H)
B10-X00-M00(C01)-D57	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, 2 H) 3.01 (t, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 4.92 (d, 2 H) 6.92 (d, 2 H) 7.57 (m, 6 H) 7.85 (m, 1 H) 7.96 (m, 1 H) 8.24 (m, 1 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D59	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.09 (m, 4 H) 4.32 (d, *J*=5.85 Hz, 2 H) 4.33 (s, 3 H) 5.98 (s, 2 H) 6.80 (dd, *J*=7.93, 1.59 Hz, 1 H) 6.86 (d, *J*=7.80 Hz, 1 H) 6.91 (d, *J*=2.56 Hz, 1 H) 6.91 (d, *J*=8.05 Hz, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.63 (t, *J*=6.40 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (d, *J*=7.07 Hz, 3 H) 2.27 (s, 3 H) 2.51 (m, 4 H) 2.78 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.74 Hz, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.15 (t, *J*=8.96 Hz, 2 H) 7.46 (dd, *J*=8.54, 5.61 Hz, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.49 (d, *J*=8.41 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D74	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.92 (m, 2 H) 1.18 (m, 4 H) 1.67 (m, 5 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, 2 H) 2.98 (t, 2 H) 3.08 (m, 6 H) 4.33 (s, 3 H) 6.92 (d, 2 H) 7.53 (d, 2 H) 8.05 (t, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (m, 4 H) 2.24 (s, 3 H) 2.52 (m, 8 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.08 (m, 4 H) 4.36 (s, 3 H) 5.11 (m, 1 H) 6.92 (d, 2 H) 7.33 (m, 3 H) 7.41 (m, 2 H) 7.52 (d, 2 H) 8.34 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, *J*=7.80 Hz, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.53 (d, *J*=7.80 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.38 (m, 1 H) 7.47 (m, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 7.86 (s, 1 H) 8.12 (d, *J*=7.80 Hz, 1 H) 8.35 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.53 (m, 10 H) 2.80 (t, 2 H) 2.95 (m, 4 H) 3.10 (m, 4 H) 3.58 (m, 4 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 6.94 (d, 2 H) 7.26 (m, 1 H) 7.35 (m, 2 H) 7.44 (m, 2 H) 7.55 (d, 2 H) 8.36 (s, 1 H) 8.42 (d, 1 H) 9.28 (s, 1 H)
B10-X00-M00(C01)-D62	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.98 (t, *J*=7.56 Hz, 2 H)

	3.09 (m, 4 H) 4.35 (s, 3 H) 6.36 (d, *J*=8.78 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.28 (m, 2 H) 7.36 (t, *J*=7.50 Hz, 4 H) 7.41 (m, 4 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.70 (d, *J*=8.90 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D75	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (m, 11 H) 1.12 (d, *J*=6.83 Hz, 3 H) 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.62 Hz, 2 H) 2.95 (m, 2 H) 3.09 (m, 4 H) 3.82 (m, 1 H) 4.33 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 7.65 (d, *J*=9.27 Hz, 1 H) 8.35 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D46	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.50 (m, 4 H) 2.78 (t, *J*=7.80 Hz, 2 H) 2.96 (m, 2 H) 3.09 (m, 4 H) 3.30 (s, 3 H) 3.60 (dd, *J*=9.94, 5.18 Hz, 1 H) 3.78 (dd, *J*=10.00, 7.93 Hz, 1 H) 4.37 (s, 3 H) 5.23 (m, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.30 (m, 3 H) 7.43 (m, 2 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.41 (d, *J*=8.54 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D56	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 (m, 6 H) 2.04 (m, 4 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.78 (t, *J*=7.68 Hz, 2 H) 2.91 (t, *J*=7.80 Hz, 2 H) 3.08 (m, 4 H) 4.37 (s, 3 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.28 (m, 5 H) 7.42 (s, 1 H) 7.54 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D69	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.86 (m, 4 H) 2.25 (s, 3 H) 2.49 (m, 4 H) 2.77 (m, 2 H) 2.83 (t, *J*=7.68 Hz, 2 H) 3.03 (m, 2 H) 3.08 (m, 4 H) 4.31 (s, 3 H) 5.20 (m, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.16 (m, 4 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.14 (d, *J*=9.02 Hz, 1 H) 8.36 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D63	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.49 (m, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.68 Hz, 2 H) 3.08 (m, 4 H) 3.15 (t, *J*=8.66 Hz, 2 H) 4.33 (m, 2 H) 4.33 (s, 3 H) 4.50 (t, *J*=8.72 Hz, 2 H) 6.69 (d, *J*=8.17 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.05 (dd, *J*=8.11, 1.89 Hz, 1 H) 7.20 (d, *J*=1.22 Hz, 1 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.35 (s, 1 H) 8.56 (t, *J*=6.34 Hz, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D65	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.60 (m, 4 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.93 (m, 4 H) 3.08 (m, 4 H) 4.32 (s, 3 H) 5.52 (q, *J*=8.17 Hz, 1 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.24 (m, 4 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.27 (d, *J*=8.66 Hz, 1 H) 8.36 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (m, 4 H) 2.26 (s, 3 H) 2.52 (m, 4 H) 2.79 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 4.35 (s, 3 H) 6.93 (d, 2 H) 7.16 (m, 1 H) 7.25 (m, *J*=10.00 Hz, 4 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.86 (s, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D66	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 (s, 6 H) 2.24 (s, 3 H) 2.50 (m, 4 H) 2.76 (t, 2 H) 2.88 (t, 2 H) 3.08 (m,

	4 H) 4.37 (s, 3 H) 6.93 (d, 2 H) 7.37 (m, 2 H) 7.52 (d, 2 H) 8.04 (s, 1 H) 8.33 (s, 1 H) 8.48 (m, 2 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D55	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 4.35 (s, 3 H) 4.48 (d, 2 H) 6.93 (d, 2 H) 7.18 (m, 2 H) 7.31 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.68 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.75 (s, 3 H) 4.34 (s, 3 H) 4.39 (d, 2 H) 6.83 (m, 1 H) 6.90 (m, 4 H) 7.24 (t, 1 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.67 (t, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D48	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.47 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.08 (m, 4 H) 3.85 (s, 3 H) 4.35 (s, 3 H) 4.41 (d, 2 H) 6.92 (m, 3 H) 7.01 (m, 1 H) 7.17 (m, 1 H) 7.24 (m, 1 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.38 (t, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D77	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J*=7.56 Hz, 6 H) 2.29 (s, 3 H) 2.55 (m, 4 H) 2.56 (q, *J*=7.68 Hz, 4 H) 2.83 (t, *J*=7.62 Hz, 2 H) 3.00 (t, *J*=7.62 Hz, 2 H) 3.11 (m, 4 H) 4.40 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.14 (d, *J*=7.68 Hz, 2 H) 7.22 (dd, *J*=8.29, 6.83 Hz, 1 H) 7.56 (d, *J*=9.02 Hz, 2 H) 8.37 (s, 1 H) 9.28 (s, 1 H) 9.57 (s, 1 H)
B10-X00-M00(C01)-D58	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.51 (m, 4 H) 2.80 (t, *J*=7.74 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.08 (m, 4 H) 3.73 (s, 6 H) 4.34 (s, 3 H) 4.36 (d, *J*=6.71 Hz, 2 H) 6.38 (t, *J*=2.32 Hz, 1 H) 6.50 (d, *J*=2.19 Hz, 2 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.54 (d, *J*=9.15 Hz, 2 H) 8.35 (s, 1 H) 8.64 (t, *J*=6.28 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D20	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.84 (t, *J*=7.74 Hz, 2 H) 3.05 (t, *J*=7.74 Hz, 2 H) 3.09 (m, 4 H) 4.41 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.10 (tt, *J*=7.39, 1.14 Hz, 1 H) 7.34 (dd, *J*=8.29, 7.56 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 7.83 (dd, *J*=8.66, 1.10 Hz, 2 H) 8.38 (s, 1 H) 9.28 (s, 1 H) 10.07 (s, 1 H)
B10-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.27 (s, 3 H) 2.52 (m, 10 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.12 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.53 (d, 2 H) 8.34 (m, 2 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D70	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.79 (t, 2 H) 2.97 (t, 2 H) 3.09 (m, 4 H) 3.35 (m, 4 H) 3.65 (dd, 1 H) 3.90 (dd, 1 H) 4.37 (s, 3 H) 5.25 (m, 1 H) 6.92 (d, *J*=8.78 Hz, 2 H) 7.29 (m, 1 H) 7.37 (m, 2 H) 7.47 (m, 2 H) 7.53 (d, 2 H) 8.35 (s, 1 H) 8.82 (d, 1 H) 9.26 (s, 1 H)
B10-X00-M00(C01)-D73	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.81 (m, 4 H) 3.11 (m, 6 H) 3.34 (m, 4 H) 4.33 (s, 3 H) 4.52 (m, 1 H) 5.38 (m, 1 H) 5.44 (d, 1 H) 6.92 (d, 2 H) 7.22

	(m, 3 H) 7.53 (d, 2 H) 7.70 (m, 1 H) 8.38 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D165	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.04 (s, 3 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.74 (t, 2 H) 2.87 (t, 2 H) 3.09 (m, 4 H) 3.35 (m, 8 H) 4.34 (s, 3 H) 6.92 (d, 2 H) 7.31 (m, 1 H) 7.43 (m, 4 H) 7.52 (d, 2 H) 8.32 (s, 1 H) 9.10 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C01)-D144	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (s, 3 H) 2.24 (m, 7 H) 2.47 (m, 4 H) 2.78 (m, 6 H) 3.08 (m, 4 H) 3.46 (m, 2 H) 3.55 (m, 2 H) 4.37 (s, 3 H) 6.93 (d, 2 H) 7.21 (m, 1 H) 7.35 (m, 4 H) 7.54 (d, 2 H) 8.35 (m, 2 H) 9.27 (s, 1 H)
B10-X00-M00(C01)-D164	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.96 (t, 2 H) 3.09 (m, 4 H) 3.55 (m, 8 H) 4.34 (s, 3 H) 6.00 (d, 1 H) 6.92 (d, 2 H) 7.34 (m, 1 H) 7.43 (m, 4 H) 7.52 (d, 2 H) 8.24 (d, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B109-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.53 (m, 4 H) 2.83 (m, 2 H) 3.00 (m, 6 H) 4.36 (s, 3 H) 4.44 (d, *J*=6.34 Hz, 2 H) 7.01 (dd, *J*=9.94, 8.96 Hz, 1 H) 7.27 (m, 5 H) 7.37 (dd, *J*=8.29, 2.19 Hz, 1 H) 7.67 (dd, *J*=15.36, 2.44 Hz, 1 H) 8.41 (s, 1 H) 8.71 (t, *J*=6.34 Hz, 1 H) 9.55 (s, 1 H)
B109-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.54 (m, 4 H) 2.82 (t, *J*=7.68 Hz, 2 H) 2.99 (m, 6 H) 4.36 (s, 3 H) 4.41 (d, *J*=6.34 Hz, 2 H) 7.01 (dd, *J*=9.94, 8.96 Hz, 1 H) 7.15 (t, *J*=8.96 Hz, 2 H) 7.37 (m, 3 H) 7.67 (dd, *J*=15.43, 2.38 Hz, 1 H) 8.41 (s, 1 H) 8.75 (t, *J*=6.28 Hz, 1 H) 9.55 (s, 1 H)
B108-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 2.71 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.34 (s, 3 H) 6.91 (d, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.51 d, 2 H) 8.34 (s, 1 H) 9.24 (s, 1 H)
B108-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 9 H) 2.71 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.34 (s, 3 H) 4.42 (d, 2 H) 6.91 (d, 2 H) 7.34 (m, 5 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.24 (s, 1 H)
B108-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 2.69 (m, 4 H) 2.80 (t, 2 H) 2.99 (t, 2 H) 3.06 (m, 4 H) 4.36 (s, 3 H) 4.44 (d, 2 H) 6.92 (d, 2 H) 7.31 (m, 2 H) 7.54 (d, 2 H) 8.35 (s, 1 H) 8.50 (m, 2 H) 8.86 (t, 1 H) 9.26 (s, 1 H)
B108-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (s, 9 H) 1.70 (s, 6 H) 2.69 (m, 4 H) 2.77 (t, 2 H) 2.90 (t, 2 H) 3.06 (m, 4 H) 4.36 (s, 3 H) 6.92 (d, 2 H) 7.20 (m, 1 H) 7.32 (m, 2 H) 7.41 (m, 2 H) 7.51 (d, 2 H) 7.79 (s, 1 H) 8.33 (s, 1 H) 9.25 (s, 1 H)
B108-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (s, 9 H) 2.69

	(s, 4 H) 2.79 (t, *J*=7.68 Hz, 2 H) 2.95 (t, *J*=7.86 Hz, 2 H) 3.08 (s, 4 H) 4.37 (s, 3 H) 5.53 (d, *J*=7.80 Hz, 1 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.31 (m, 1 H) 7.38 (m, 3 H) 7.47 (d, *J*=7.19 Hz, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 7.87 (s, 1 H) 8.12 (d, *J*=7.68 Hz, 1 H) 8.34 (s, 1 H) 9.26 (s, 1 H)
B108-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (s, 9 H) 2.52 (m, 4 H) 2.68 (m, 4 H) 2.78 (t, 2 H) 2.92 (m, 4 H) 3.07 (m, 4 H) 3.56 (m, 4 H) 4.37 (s, 3 H) 5.16 (m, 1 H) 6.92 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.51 (d, 2 H) 8.34 (s, 1 H) 8.40 (d, 1 H) 9.25 (s, 1 H)
B108-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (s, 9 H) 2.66 (s, 4 H) 2.80 (t, *J*=7.68 Hz, 2 H) 2.99 (t, *J*=7.62 Hz, 2 H) 3.06 (s, 4 H) 3.75 (s, 3 H) 4.34 (s, 3 H) 4.40 (d, *J*=6.22 Hz, 2 H) 6.82 (ddd, *J*=8.20, 2.59, 0.91 Hz, 1 H) 6.90 (m, 4 H) 7.24 (t, *J*=8.05 Hz, 1 H) 7.53 (d, *J*=8.90 Hz, 2 H) 8.35 (s, 1 H) 8.67 (t, *J*=6.34 Hz, 1 H) 9.25 (s, 1 H)
B19-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (t, 2 H) 3.00 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.34 (s, 3 H) 4.44 (d, 2 H) 6.94 (d, 2 H) 7.34 (m, 5 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.69 (t, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D21	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (t, 2 H) 2.99 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.34 (s, 3 H) 4.41 (d, 2 H) 6.94 (d, 2 H) 7.15 (m, 2 H) 7.36 (m, 2 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.74 (t, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D24	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (d, 3 H) 2.79 (t, 2 H) 2.96 (t, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (d, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.55 (d, 2 H) 8.35 (s, 1 H) 8.42 (d, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D47	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.78 (m, 2 H) 2.96 (m, 2 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (m, 2 H) 7.24 (t, 1 H) 7.33 (t, 2 H) 7.41 (m, 2 H) 7.55 (m, 2 H) 8.35 (s, 1 H) 8.42 (s, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D42	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.90 (m, 4 H) 3.05 (m, 4 H) 3.76 (m, 4 H) 4.35 (s, 3 H) 4.40 (m, 2 H) 6.94 (m, 2 H) 7.37 (m, 3 H) 7.55 (m, 2 H) 8.36 (s, 1 H) 8.81 (m, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D41	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.89 (m, 3 H) 1.81 (m, 2 H) 2.78 (m, 4 H) 3.05 (m, 4 H) 3.76 (m, 4 H) 4.36 (s, 3 H) 4.88 (m, 1 H) 6.93 (m, 2 H) 7.23 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.55 (m, 2 H) 8.34 (m, 1 H) 8.37 (d, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D68	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.81 (m, 2 H) 2.78 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.36 (s, 3 H) 4.88 (m, 1 H) 6.93 (m, 2 H) 7.33 (m, 5 H) 7.55 (m, 2 H) 8.34 (m, 1 H) 8.40 (m, 1 H) 9.27 (m, 1 H)

B19-X00-M00(C01)-D61	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.51 (m, 3 H) 2.96 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 5.15 (m, 1 H) 6.94 (m, 2 H) 7.33 (m, 5 H) 7.55 (m, 2 H) 8.35 (s, 1 H) 8.42 (m, 1 H) 9.27 (m, 1 H)
B19-X00-M00(C01)-D40	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (m, 4 H) 3.05 (m, 4 H) 3.75 (m, 4 H) 4.35 (s, 3 H) 4.43 (m, 2 H) 6.94 (d, 2 H) 7.18 (m, 4 H) 7.55 (d, 2 H) 8.36 (s, 1 H) 8.79 (s, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (t, *J*=7.68 Hz, 2 H) 2.96 (t, *J*=7.74 Hz, 2 H) 3.05 (m, 4 H) 3.74 (m, 6 H) 4.37 (s, 3 H) 5.02 (m, 2 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.39 (m, 2 H) 7.56 (d, *J*=9.02 Hz, 2 H) 8.27 (d, *J*=8.29 Hz, 1 H) .35 (s, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.01 (m, 4 H) 3.07 (s, 4 H) 3.77 (m, 4 H) 4.38 (m, 3 H) 4.46 (m, 2 H) 6.95 (m, 1 H) 7.33 (m, 2 H) 7.57 (m, 2 H) 8.38 (s, 1 H) 8.58 (m, 2 H) 8.88 (m, 1 H) 9.31 (s, 1 H)
B19-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.77 (t, *J*=7.80 Hz, 2 H) 2.90 (m, 2 H) 3.06 (m, 4 H) 3.76 (m, 4 H) 4.36 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.20 (m, 1 H) 7.32 (t, *J*=7.68 Hz, 2 H) 7.42 (m, 2 H) 7.56 (d, *J*=9.15 Hz, 2 H) 7.79 (s, 1 H) 8.34 (s, 1 H) 9.27 (s, 1 H)
B19-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 5 H) 2.78 (m, 5 H) 3.05 (m, 4 H) 3.56 (m, 4 H) 3.76 (m, 4 H) 4.37 (s, 3 H) 5.17 (m, 1 H) 7.30 (m, 9 H) 8.34 (m, 1 H) 8.40 (m, 1 H) 9.28 (s, 1 H)
B19-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 (m, 4 H) 3.06 (m, 4 H) 3.76 (m, 4 H) 4.37 (s, 3 H) 5.54 (m, 1 H) 6.94 (m, 2 H) 7.42 (m, 8 H) 7.86 (m, 1 H) 8.11 (d, 1 H) 8.35 (m, 1 H) 9.28 (m, 1 H)
B19-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 (m, 4 H) 2.52 (s, 6 H) 2.87 (d, 4 H) 3.05 (s, 4 H) 3.76 (s, 4 H) 4.37 (s, 3 H) 5.10 (m, 1 H) 7.30 (m, 9 H) 8.35 (m, 2 H) 9.28 (m, 1 H)
B09-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 4 H) 2.82 (t, 2 H) 3.00 (t, 2 H) 3.13 (m, 4 H) 3.75 (s, 3 H) 4.36 (s, 3 H) 4.40 (d, 2 H) 6.59 (m, 1 H) 6.83 (m, 1 H) 6.90 (m, 2 H) 7.14 (m, 1 H) 7.24 (m, 3 H) 8.40 (s, 1 H) 8.67 (t, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 3 H) 2.52 (m, 4 H) 2.80 (t, 2 H) 2.97 (t, 2 H) 3.13 (m, 4 H) 3.73 (m, 2 H) 4.39 (s, 3 H) 5.00 (m, 2 H) 6.59 (m, 1 H) 7.14 (m, 1 H) 7.25 (m, 7 H) 8.26 (d, 1 H) 8.40 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.28 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.14 (m, 4 H) 4.37 (s, 3 H) 6.59 (m, 1 H) 6.71 (m, 1 H) 7.24 (m, 7

	H) 8.40 (s, 1 H) 8.86 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (m, 4 H) 2.25 (s, 3 H) 2.48 (m, 4 H) 2.83 (m, 10 H) 3.12 (m, 4 H) 4.38 (s, 3 H) 5.10 (m, 1 H) 6.58 (ddd, *J*=8.14, 2.29, 0.67 Hz, 1 H) 7.14 (t, *J*=7.99 Hz, 1 H) 7.24 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.35 (d, *J*=8.66 Hz, 1 H) 8.39 (s, 1 H) 9.33 (s, 1 H)
B09-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.52 (m, 4 H) 2.81 (t, *J*=7.80 Hz, 2 H) 2.97 (m, 2 H) 3.14 (m, 4 H) 4.39 (s, 3 H) 5.53 (d, *J*=7.68 Hz, 1 H) 6.58 (dd, *J*=8.11, 2.26 Hz, 1 H) 7.14 (t, *J*=8.05 Hz, 1 H) 7.26 (m, 2 H) 7.31 (m, 1 H) 7.38 (m, 3 H) 7.48 (m, 2 H) 7.87 (s, 1 H) 8.12 (d, *J*=7.68 Hz, 1 H) 8.40 (s, 1 H) 9.34 (s, 1 H)
B09-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.29 (s, 3 H) 2.49 (m, 8 H) 2.80 (t, *J*=7.68 Hz, 3 H) 2.97 (m, 3 H) 3.14 (m, 4 H) 4.39 (s, 3 H) 5.14 (m, 1 H) 6.58 (dd, *J*=8.17, 1.83 Hz, 1 H) 7.15 (t, *J*=8.11 Hz, 1 H) 7.26 (m, 3 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.41 (m, 2 H) 8.36 (s, 1 H) 8.40 (s, 1 H) 9.34 (s, 1 H)
B101-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.83 (t, 2 H) 3.01 (t, 2 H) 3.40 (s, 2 H) 4.36 (s, 3 H) 4.43 (d, 2 H) 7.23 (m, 3 H) 7.34 (m, 3 H) 7.65 (d, 2 H) 8.41 (s, 1 H) 8.71 (t, 1 H) 9.50 (s, 1 H)
B101-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.83 (t, 2 H) 3.00 (t, 2 H) 3.40 (s, 2 H) 4.38 (s, 3 H) 4.44 (d, 2 H) 7.23 (d, 2 H) 7.30 (m, 2 H) 7.65 (d, 2 H) 8.41 (s, 1 H) 8.50 (m, 2 H) 8.87 (t, 1 H) 9.51 (s, 1 H)
B101-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.16 (s, 3 H) 2.34 (m, 8 H) 2.79 (t, 2 H) 2.91 (t, 2 H) 3.40 (s, 2 H) 4.38 (s, 3 H) 7.21 (m, 3 H) 7.32 (m, 2 H) 7.42 (m, 2 H) 7.64 (d, 2 H) 7.80 (s, 1 H) 8.39 (s, 1 H) 9.50 (s, 1 H)
B101-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 (d, 3 H) 2.16 (s, 3 H) 2.34 (m, 8 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.41 (m, 2 H) 4.37 (s, 3 H) 5.15 (m, 1 H) 7.15 (dd, 2 H) 7.23 (d, 2 H) 7.46 (dd, 2 H) 7.64 (d, 2 H) 8.40 (s, 1 H) 8.50 (d, 1 H) 9.49 (s, 1 H)
B101-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H) 2.34 (m, 8 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.40 (s, 2 H) 4.39 (s, 3 H) 5.52 (d, 1 H) 7.23 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 4 H) 7.46 (m, 2 H) 7.64 (d, 2 H) 7.87 (s, 2 H) 8.12 (d, 1 H) 8.40 (s, 1 H) 9.50 (s, 1 H)
B102-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.36 (m, 4 H) 2.83 (t, *J*=7.74 Hz, 2 H) 3.01 (t, *J*=7.68 Hz, 2 H) 3.43 (m, 2 H) 3.59 (m, 4 H) 4.36 (s, 3 H) 4.44 (d, *J*=6.46 Hz, 2 H) 7.25 (m, 3 H) 7.32 (m, 4 H) 7.68 (d, *J*=8.17 Hz, 2 H) 8.41 (s, 1 H) 8.71 (t, *J*=6.28 Hz, 1 H) 9.52 (s, 1 H)
B102-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 10 H)

	2.81 (t, 2 H) 2.95 (t, 2 H) 3.43 (s, 2 H) 3.59 (m, 8 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 7.25 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.66 (d, 2 H) 8.40 (m, 2 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 2.36 (m, 4 H) 2.79 (t, 2 H) 2.91 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.38 (s, 3 H) 7.25 (m, 3 H) 7.32 (m, 2 H) 7.42 (m, 2 H) 7.66 (d, 2 H) 7.80 (s, 1 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.54 (d, 1 H) 7.25 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.46 (m, 2 H) 7.66 (d, 2 H) 7.87 (s, 2 H) 8.12 (d, 1 H) 8.41 (s, 1 H) 9.52 (s, 1 H)
B102-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (m, 4 H) 2.37 (m, 4 H) 2.82 (t, 2 H) 2.97 (t, 2 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 4.37 (s, 3 H) 7.16 (m, 1 H) 7.24 (m, 6 H) 7.66 (d, 2 H) 8.40 (s, 1 H) 8.87 (s, 1 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (m, 4 H) 2.36 (m, 4 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.35 (m, 6 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.11 (m, 1 H) 7.25 (m, 3 H) 7.35 (m, 2 H) 7.43 (m, 2 H) 7.66 (d, 2 H) 8.40 (m, 2 H) 9.51 (s, 1 H)
B102-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.38 (m, 10 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.42 (s, 2 H) 3.59 (m, 4 H) 4.39 (s, 3 H) 5.11 (m, 1 H) 7.25 (m, 3 H) 7.33 (m, 2 H) 7.40 (m, 2 H) 7.66 (d, 2 H) 8.35 (d, 1 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B105-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.92 (m, 4 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 3.75 (s, 3 H) 4.39 (m, 5 H) 6.90 (m, 4 H) 7.25 (m, 2 H) 7.57 (m, 1 H) 7.77 (m, 1 H) 8.42 (m, 1 H) 8.68 (s, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.90 (m, 4 H) 3.44 (m, 2 H) 3.59 (m, 4 H) 4.42 (s, 3 H) 5.53 (m, 1 H) 6.93 (m, 1 H) 7.47 (m, 8 H) 7.82 (m, *J*=39.51 Hz, 2 H) 8.12 (m, 1 H) 8.42 (m, 1 H) 9.55 (m, 1 H)
B105-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.09 (m, 4 H) 2.38 (m, 4 H) 2.90 (m, 4 H) 3.45 (m, 4 H) 3.59 (m, 4 H) 4.42 (s, 3 H) 6.93 (m, 1 H) 7.25 (m, 7 H) 7.57 (m, 1 H) 7.76 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (m, 4 H) 2.90 (m, 4 H) 3.45 (m, 2 H) 3.60 (m, 4 H) 3.73 (m, 2 H) 4.42 (m, 3 H) 5.00 (m, 2 H) 6.92 (m, 1 H) 7.32 (m, 6 H) 7.57 (m, 1 H) 7.77 (m, 1 H) 8.27 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B105-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.38 (m, 4 H) 2.98 (m, 4 H) 3.44 (m, 2 H) 3.60 (m, 4 H) 4.40 (s, 3 H) 6.92 (m, 1 H) 7.20 (m, 6 H) 7.58 (m, 1 H) 7.77 (s, 1 H) 8.42 (s, 1 H) 9.20 (m, 2 H)

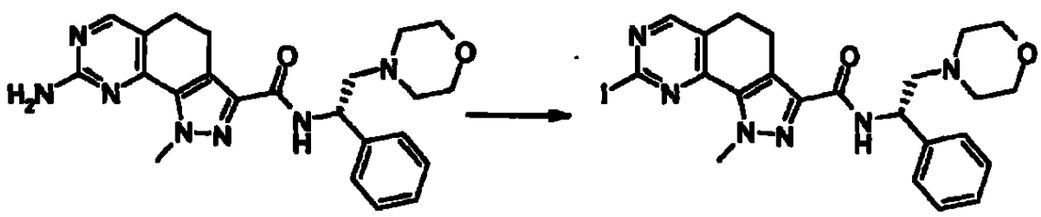
B105-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 (m, 6 H) 2.52 (m, 8 H) 2.81 (m, 4 H) 3.45 (m, 2 H) 3.60 (s, 4 H) 4.42 (s, 3 H) 5.11 (m, 1 H) 6.92 (m, 1 H) 7.25 (m, 6 H) 7.57 (m, 1 H) 7.76 (m, 1 H) 8.34 (m, 1 H) 8.42 (m, 1 H) 9.54 (m, 1 H)
B104-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (s, 6 H) 2.21 (s, 3 H) 2.40 (m, 8 H) 2.80 (t, 2 H) 2.92 (t, 2 H) 3.44 (s, 2 H) 4.40 (s, 3 H) 6.91 (m, 1 H) 7.32 (m, 4 H) 7.42 (m, 2 H) 7.55 (m, 1 H) 7.75 (m, 1 H) 7.81 (m, 1 H) 8.41 (s, 1 H) 9.53 (s, 1 H)
B104-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 4 H) 2.20 (m, 3 H) 2.40 (m, 8 H) 2.82 (t, 2 H) 2.98 (t, 2 H) 3.44 (s, 2 H) 4.39 (s, 3 H) 6.90 (m, 1 H) 7.25 (m, 6 H) 7.56 (m, 1 H) 7.76 (m, 1 H) 8.42 (s, 1 H) 8.87 (s, 1 H) 9.53 (s, 1 H)
B104-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.42 (m, 8 H) 2.82 (t, 2 H) 2.97 (t, 2 H) 3.44 (s, 2 H) 4.41 (s, 3 H) 5.53 (d, 1 H) 6.91 (d, 1 H) 7.24 (m, 1 H) 7.38 (m, 3 H) 7.46 (m, 2 H) 7.56 (m, 1 H) 7.75 (m, 1 H) 7.87 (s, 2 H) 8.12 (m, 1 H) 8.42 (s, 1 H) 9.54 (s, 1 H)
B104-X00-M00(C01)-D35	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 2.39 (m, 8 H) 2.83 (t, 2 H) 3.01 (t, 2 H) 3.43 (s, 2 H) 3.75 (s, 3 H) 4.38 (s, 3 H) 4.41 (d, 2 H) 6.83 (m, 1 H) 6.90 (m, 3 H) 7.24 (m, 2 H) 7.56 (m, 1 H) 7.76 (m, 1 H) 8.42 (s, 1 H) 8.68 (t, 1 H) 9.53 (s, 1 H)
B103-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 (m, 1 H) 1.95 (m, 1 H) 2.09 (m, 1 H) 2.26 (m, 1 H) 2.82 (m, 5 H) 3.00 (t, 2 H) 3.34 (m, 4 H) 4.34 (s, 3 H) 4.43 (d, 2 H) 4.65 (m, 1 H) 7.02 (m, 2 H) 7.25 (m, 1 H) 7.33 (m, 4 H) 7.62 (m, 2 H) 8.38 (s, 1 H) 8.67 (t, 1 H) 9.39 (s, 1 H)
B103-X00-M00(C01)-D52	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.70 (s, 6 H) 1.79 (m, 2 H) 2.00 (m, 2 H) 2.56 (s, 3 H) 2.68 (m, 2 H) 2.78 (t, 2 H) 2.90 (t, 2 H) 2.99 (m, 2 H) 4.35 (s, 3 H) 4.42 (m, 1 H) 6.97 (d, 2 H) 7.21 (m, 1 H) 7.32 (m, 2 H) 7.41 (m, 2 H) 7.58 (d, 2 H) 7.78 (s, 1 H) 8.35 (s, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D37	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.48 (d, 3 H) 1.84 (m, 2 H) 2.01 (m, 2 H) 2.79 (m, 4 H) 2.96 (m, 4 H) 4.34 (s, 3 H) 4.43 (m, 1 H) 5.15 (m, 1 H) 6.97 (d, 2 H) 7.15 (m, 2 H) 7.46 (m, 2 H) 7.58 (d, 2 H) 8.36 (s, 1 H) 8.47 (d, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D51	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71 (m, 2 H) 1.96 (m, 2 H) 2.34 (s, 3 H) 2.42 (m, 2 H) 2.79 (m, 6 H) 4.36 (m, 4 H) 5.52 (d, 1 H) 6.94 (d, 2 H) 7.31 (m, 1 H) 7.38 (m, 2 H) 7.46 (m, 2 H) 7.56 (d, 2 H) 7.87 (s, 2 H) 8.11 (d, 1 H) 8.36 (s, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.69 (m, 2 H) 1.94 (m, 2 H) 2.32 (s, 3 H) 2.39 (m, 2 H) 2.80 (m, 4 H) 2.99 (t, 2 H) 4.35 (m, 4 H) 4.44 (d, 2 H) 6.94 (d, 2 H) 7.31 (m, 2

	H) 7.57 (d, 2 H) 8.37 (s, 1 H) 8.50 (m, 2 H) 8.85 (t, 1 H) 9.34 (s, 1 H)
B103-X00-M00(C01)-D36	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 (m, 4 H) 2.20 (m, 3 H) 2.37 (m, 4 H) 2.55 (m, 4 H) 2.88 (m, *J*=59.63 Hz, 6 H) 4.28 (m, 1 H) 4.35 (s, 3 H) 5.10 (m, 1 H) 5.35 (none, 1 H) 6.93 (m, 2 H) 7.31 (m, 5 H) 7.56 (m, 2 H) 8.35 (m, 2 H) 9.32 (m, 6 H)
B103-X00-M00(C01)-D39	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.68 (s, 4 H) 1.91 (m, 4 H) 2.20 (m, 3 H) 2.52 (m, 8 H) 2.87 (m, *J*=66.33 Hz, 4 H) 3.04 (m, 2 H) 4.28 (m, 1 H) 4.35 (s, 3 H) 5.08 (m, 1 H) 6.93 (m, 2 H) 7.38 (m, 7 H) 8.35 (m, 2 H) 9.32 (m, 1 H)
B103-X00-M00(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.78 (m, *J*=106.57 Hz, 4 H) 2.41 (m, 7 H) 2.87 (m, *J*=68.16 Hz, 4 H) 3.73 (m, 2 H) 4.28 (m, 1 H) 4.36 (s, 3 H) 5.00 (m, 2 H) 6.93 (m, 2 H) 7.32 (m, 5 H) 7.56 (m, 2 H) 8.26 (m, 1 H) 8.36 (m, 1 H) 9.32 (m, 1 H)
B103-X00-M00(C01)-D43	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (m, 4 H) 1.79 (m, *J*=107.43 Hz, 4 H) 2.43 (m, 7 H) 2.88 (m, *J*=66.33 Hz, 4 H) 4.29 (m, 1 H) 4.34 (m, 3 H) 6.93 (m, 2 H) 7.22 (m, 5 H) 7.56 (m, 2 H) 8.36 (s, 1 H) 8.86 (m, 1 H) 9.32 (m, 1 H)
B00-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.71 (t, 2 H) 2.90 (t, 2 H) 3.57 (m, 4 H) 4.36 (m, 3 H) 5.15 (m, 1 H) 6.55 (s, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 8.17 (s, 1 H) 8.36 (d, 1 H).
B00-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.71 (t, 2 H) 2.94 (t, 2 H) 4.35 (s, 3 H) 4.43 (d, 2 H) 6.56 (s, 2 H) 7.31 (m, 2 H) 8.18 (s, 1 H) 8.50 (m, 2 H) 8.82 (t, 1 H).
B113-X00-M00(C01)-D44	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.83 (t, 2 H) 3.00 (t, 2 H) 4.35 (s, 3 H) 4.44 (d, 2 H) 7.16 (m, 2 H) 7.30 (m, 2 H) 7.71 (m, 2 H) 8.41 (s, 1 H) 8.50 (m, 2 H) 8.87 (t, 1 H) 9.55 (s, 1 H)
B112-X00-M00(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.84 (t, *J*=7.68 Hz, 2 H) 3.01 (t, *J*=7.68 Hz, 2 H) 4.35 (s, 3 H) 4.44 (d, *J*=6.34 Hz, 2 H) 7.26 (m, 5 H) 7.36 (d, *J*=9.02 Hz, 2 H) 7.76 (d, *J*=9.02 Hz, 2 H) 8.44 (s, 1 H) 8.72 (t, *J*=6.40 Hz, 1 H) 9.68 (s, 1 H)
B04-X04-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.87 (t, 2 H) 2.99 (t, 2 H) 3.71 (s, 3 H) 7.25 (m, 1 H) 7.44 (s, 1 H) 7.51 (m, 3 H) 7.66 (m, 2 H) 8.55 (s, 1 H)
B10-X00-M04(C15)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (m, 6 H) 3.05 (m, 4 H) 3.33 (m, 5 H) 6.28 (s, 2 H) 6.80 (d, 2 H) 7.33 (s, 2 H) 7.47 (m, 7 H) 7.63 (d, 2 H) 7.66 (s, 1 H) 8.42 (s, 1 H) 9.34 (s, 1 H)
B09-X00-M04(C03)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.79 (m, 9 H) 1.64 (t, 2 H) 2.86 (m, 15 H) 4.84 (t, 2 H) 6.67 (m, 1 H) 7.21

	(m, 3 H) 7.39 (s, 2 H) 8.41 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C14)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (t, 3 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.61 (q, 2 H) 2.84 (t, 2 H) 3.03 (m, 6 H) 6.16 (s, 2 H) 6.75 (d, 2 H) 6.83 (s, 1 H) 7.29 (br. s, 2 H) 7.36 (d, 2 H) 7.45 (br. s, 1 H) 8.38 (s, 1 H) 9.25 (s, 1 H)
B10-X00-M00(C14)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, 3 H) 2.24 (s, 3 H) 2.46 (m, 4 H) 2.60 (q, 2 H) 2.85 (t, 2 H) 3.02 (m, 6 H) 4.41 (d, 2 H) 6.18 (s, 2 H) 6.74 (d, 2 H) 6.83 (s, 1 H) 7.23 (m, 1 H) 7.31 (m, 4 H) 7.37 (d, 2 H) 8.38 (s, 1 H) 8.69 (t, 1 H) 9.26 (s, 1 H)
B08-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.79 (m, 2 H) 2.96 (m, 2 H) 3.83 (s, 3 H) 4.23 (s, 3 H) 6.96 (m, 3 H) 7.22 (s, 1 H) 7.43 (s, 1 H) 8.00 (m, 1 H) 8.11 (s, 1 H) 8.35 (s, 1 H)
B36-X00-M00(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (t, 2 H) 2.95 (t, 2 H) 4.28 (s, 3 H) 5.95 (s, 2 H) 6.84 (d, 1 H) 7.06 (dd, 1 H) 7.22 (s, 1 H) 7.34 (d, 1 H) 7.42 (s, 1 H) 8.34 (s, 1 H) 9.34 (s, 1 H)

Ejemplo 52

8-yodo-1-metil-N-[(1S)-2-morfolin-4-il-1-feniletil]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida



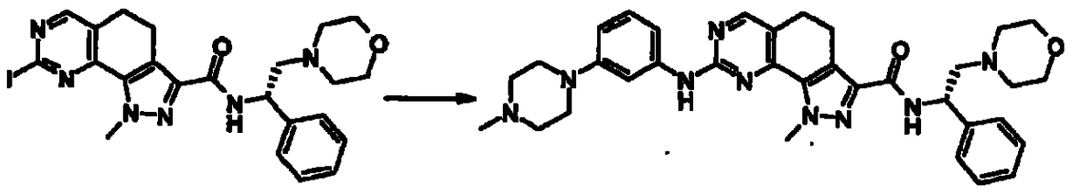
A una suspensión caliente y bien agitada de 8-amino-1-metil-N-[(1S)-2-morfolin-4-il-1-feniletil]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida (3 g, 6.92 mmol) en

dimetoxietano (240 mL), mantenida en una atmósfera inerte de argón, se agregaron en secuencia yoduro de cesio (2.16 g, 8.3 mmol), yoduro bisublimado (870 mg, 3.46 mmol), yoduro de cobre (460 mg, 2.42 mmol) y nitrito de isopentilo (1.71 mL, 1.5 g, 12.46 mmol). La mezcla de reacción se agitó vigorosamente a 65-70°C durante 18 horas. Después de enfriamiento en un baño de agua con hielo, el sólido se filtró y el filtrado se diluyó con diclorometano (100 mL), se lavó con hidróxido de amonio al 30% (50 mL), tiosulfato de sodio (100 mL), solución salina y se secaron sobre Na_2SO_4 anhidro. El crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 95:59) y se aisló 1.48 g del compuesto del título (40% de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.89 (t, 2 H) 2.99 (t, 2 H) 4.30 (s, 3 H) 5.17 (m, 1 H) 7.22 (m, 1 H) 7.34 (m, 2 H) 7.41 (m, 2 H) 8.47 (s, 1 H)

Ejemplo 53

1-metil-8-{[3-(4-metilpiperazin-1-il)fenil]amino}-N-[(1S)-2-morfolin-4-il-1-feniletil]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B09-X00-M00(C01)-D38]



Acetato de paladio [$Pd(OAc)_2$] (10 mg, 0.022 mmol, 10%), (±)-BINAP (14 mg, 0.022 mmol, 10%) y dimetilformamida (4 mL) se cargaron en un frasco de fondo redondo lavado con argón. La mezcla se agitó bajo argón durante 30 minutos. Luego se agregaron, 3-(4-metilpiperazin-1-il)fenilamina (84 mg, 0.44 mmol), 8-yodo-1-metil-N-[(1S)-2-morfolin-4-il-1-feniletil]-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida (120 mg, 0.22 mmol), carbonato de potasio (670 mg, 4.85 mmol) y dimetilformamida (1. 5 mL). La mezcla resultante se calentó a 80°C en un baño de aceite bajo argón con buena agitación durante 1.5 horas.

Después de enfriar a temperatura ambiente, la mezcla de reacción se vertió en agua y se extrajo con diclorometano. Los extractos orgánicos se lavaron con solución salina y se secaron sobre Na_2SO_4. El disolvente se removió bajo vacío, el crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 95:5) para producir 40 mg (30% de producto) del compuesto del título.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.27 (s, 3 H) 2.52 (m, 8 H) 2.80 (t, 2 H) 2.94 (m, 4 H) 3.13 (m, 4H) 3.56 (m, 4H) 4.39 (s, 3H) 5.16 (m, 1 H) 6.59 (m, 1 H) 7.14 (m, 1 H) 7.24 (m, 2 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 8.39 (m, 2 H) 9.33 (s, 1 H).

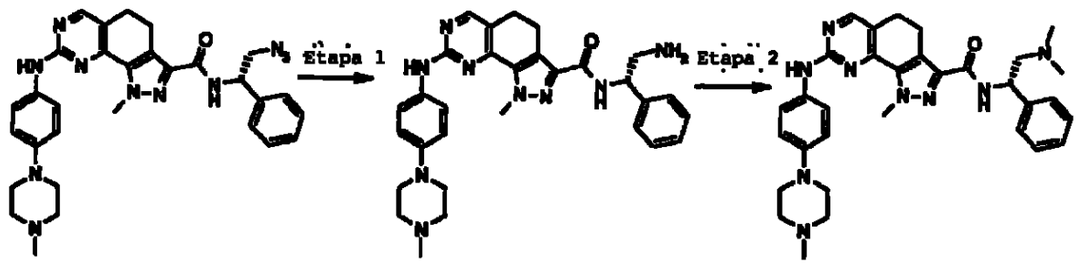
Al trabajar análogamente se prepararon los siguientes compuestos:

Tabla XIV

B107-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 6 H) 2.80 (t, 2 H) 2.97 (m, 2 H) 3.09 (m, 4 H) 3.57 (m, 4 H) 3.76 (m, 4 H) 4.39 (s, 3 H) 5.18 (m, 1 H) 6.60 (m, 1 H) 7.16 (m, 1 H) 7.42 (m, 6 H) 8.40 (m, 2 H) 9.35 (s, 1 H)
B105-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (m, 10 H) 2.81 (t, 2 H) 2.97 (t, 2 H) 3.34 (m, 10 H) 4.41 (s, 3 H)

	5.17 (m, 1 H) 6.93 (m, 1 H) 7.34 (m, 4 H) 7.42 (m, 2 H) 7.58 (m, 1 H) 7.77 (m, 1 H) 8.41 (m, 2 H) 9.54 (s, 1 H)
B103-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 (m, 2 H) 1.92 (m, 2 H) 2.21 (m, 5 H) 2.52 (m, 4 H) 2.65 (m, 2 H) 2.79 (t, 2 H) 2.95 (m, 4 H) 3.56 (m, 4 H) 4.29 (m, 1 H) 4.36 (s, 3 H) 5.17 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.56 (d, 2 H) 8.35 (s, 1 H) 8.40 (d, 1 H) 9.32 (s, 1 H)
B101-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 2.52 (m, 8 H) 2.80 (t, 2 H) 2.95 (m, 4 H) 3.33 (m, 6 H) 3.56 (m, 4 H) 4.39 (s, 3 H) 5.17 (m, 1 H) 7.23 (m, 3 H) 7.33 (m, 2 H) 7.42 (m, 2 H) 7.65 (d, 2 H) 8.40 (m, 2 H) 9.50 (s, 1 H)
B104-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H) 2.42 (m, 13 H) 2.81 (t, *J*=7.80 Hz, 2 H) 2.95 (m, 3 H) 3.44 (s, 2 H) 3.57 (m, 4 H) 4.41 (s, 3 H) 5.17 (m, 1 H) 6.90 (d, *J*=7.56 Hz, 1 H) 7.24 (t, *J*=7.68 Hz, 2 H) 7.33 (t, *J*=7.50 Hz, 2 H) 7.43 (m, 2 H) 7.57 (dd, *J*=8.29, 0.98 Hz, 1 H) 7.76 (t, *J*=1.95 Hz, 1 H) 8.41 (d, *J*=7.68 Hz, 1 H) 8.41 (s, 1 H) 9.53 (s, 1 H)
B110-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.45 (m, 6 H) 2.73 (m, 16 H) 3.57 (m, 4 H) 4.39 (s, 3 H) 5.17 (m, 1 H) 7.26 (m, 2 H) 7.25 (m, 1 H) 7.33 (t, *J*=7.56 Hz, 2 H) 7.43 (m, 2 H) 7.70 (s, 2 H) 8.42 (m, 2 H) 9.55 (s, 1 H)
B106-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 (m, 2 H) 1.98 (m, 2 H) 2.52 (m, 7 H) 2.81 (m, 8 H) 3.56 (m, 4 H) 4.41 (m, 4 H) 5.17 (m, 1 H) 6.60 (m, 1 H) 7.26 (m, 5 H) 7.44 (m, 3 H) 8.42 (m, 2 H) 9.50 (s, 1 H)
B111-X00-M00(C01)-D38	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, *J*=7.19 Hz, 3 H) 2.46 (m, 5 H) 2.80 (t, *J*=7.74 Hz, 2 H) 2.93 (m, 3 H) 3.56 (q, 4 H) 4.03 (q, *J*=7.19 Hz, 2 H) 4.20 (s, 3 H) 5.16 (m, 1 H) 6.20 (d, *J*=1.71 Hz, 1 H) 7.24 (t, *J*=7.32 Hz, 1 H) 7.33 (t, *J*=7.44 Hz, 2 H) 7.42 (m, 3 H) 8.36 (s, 1 H) 8.41 (d, *J*=6.95 Hz, 1 H) 9.23 (s, 1 H)

Ejemplo 54



Etapa 1. **N-[(1S)-2-amino-1-feniletil]-1-metil-8-{4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida** [B10-X00-M00(C01)-D71]

A una solución de 129 mg (0.228 mmol) de N-[(1S)-2-azido-1-feniletil]-1-metil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida en 16 mL de metanol, se disolvieron 65 mg (1.2 mmol) de NH_4Cl en 3.2 mL de agua y se agregaron 39 mg de hierro (0.7 mmol) y la mezcla se refluyó durante la noche. La suspensión se enfrió a temperatura ambiente y se filtro. Después de la remoción del metanol, Na_2CO_3 sólido se agregó por porciones a la fase acuosa hasta obtener un pH de 10 y el producto luego se extrajo con diclorometano. La cromatografía flash del crudo (eluente diclorometano/metanol 95/5) produjo 94 mg del compuesto del título.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.47 (m, 4 H) 2.78 (t, J=7.68 Hz, 2 H) 2.96 (m, 3 H) 3.08 (m, 5 H) 4.37 (s, 3 H) 5.01 (m, 1 H) 6.91 (d, J=9.15 Hz, 2 H) 7.31 (m, 5 H)

7.54 (d, J=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.54 (d, J=8.17 Hz, 1 H) 9.26 (s, 1 H).

Al trabajar de acuerdo con el método anterior se preparó el siguiente compuesto:

B10-X00-M03(C01)-D71

^{1}R NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 3 H) 1.34 (s, 3 H) 2.24 (s, 3 H) 2.45-2.49 (m, 4 H) 2.62-2.72 (m, 2 H) 2.90-3.05 (m, 2 H) 3.06-3.10 (m, 4 H) 4.35 (s, 3 H) 5.01 (td, J=8.20, 5.67 Hz, 1 H) 6.91 (d, J=9.15 Hz, 2 H) 7.24-7.29 (m, 1 H) 7.33-7.38 (m, 2 H) 7.38-7.41 (m, 2 H) 7.53 (d, J=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.65 (d, J=8.29 Hz, 1 H) 9.26 (s, 1 H).

Etapa 2. **N-[(1S)-2-(dimetilamino)-1-feniletil]-1-metil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida** [B10-X00-M00(C01)-D72]

A una solución de 50 mg (0.091 mmol) de N-[(1S)-2-amino-1-feniletil]-1-metil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida en metanol (5 mL), se agregaron 0.027 mL de formaldehido (solución acuosa al 40% 0.364 mmol) y ácido acético (0.02 mL). Después de 30 minutos, se agregaron 77 mg (0.364 mmol)

de sodiotriacetoxiborohidruro y la mezcla se agitó durante 5 horas. El disolvente se removió bajo vacío, el crudo se disolvió en agua y se agregó Na_2CO_3 por porciones hasta un pH básico. El producto se extrajo con diclorometano como un compuesto solo (34 mg, 66 % de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s, 9 H) 2.52 (m, 4 H) 2.78 (t, 2 H) 2.95 (t, 2 H) 3.09 (m, 4 H) 4.37 (s, 3 H) 5.11 (m, 1 H) 6.93 (d, 2 H) 7.24 (m, 1 H) 7.33 (m, 2 H) 7.41 (m, 2 H) 7.53 (d, 2 H) 8.34 (m, 2 H) 9.26 (s, 1 H).

Al trabajar análogamente se prepararon los siguientes compuestos:

1-metil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-N-{(1S)-2-[(1-metilpiperidin-4-il)amino]-1-feniletil}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B10-X00-M00(C01)-D145]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.76 (m, 4 H) 2.73 (m, 24 H) 4.39 (s, 3 H) 5.34 (m, 1 H) 6.98 (d, 2 H) 7.30 (m, 1 H) 7.38 (m, 2 H) 7.43 (m, 2 H) 7.57 (d, 2 H) 8.36 (s, 1 H) 8.75 (s, 1 H) 9.33 (bs, 1 H).

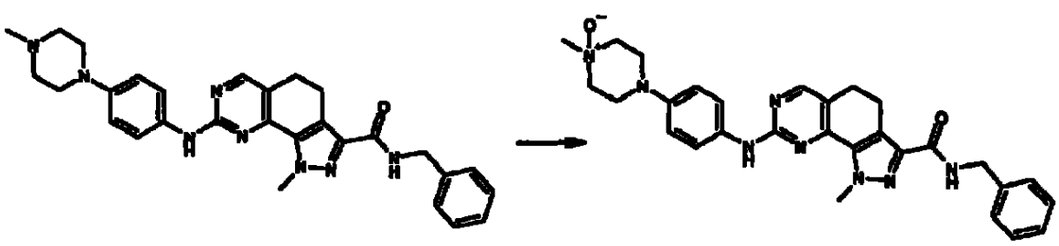
B10-X00-M03(C01)-D72

000536

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (s, 3 H) 1.32 (s, 3 H) 2.24 (s, 6 H) 2.25 (s, 3H) 2.49 (m, 4 H) 2.67 (m, 2 H) 2.80 (m, 2 H) 3.08 (m, 4 H) 4.34 (s, 3 H) 5.12 (td, J=8.20, 5.67 Hz, 1 H) 6.91 (d, J=9.15 Hz, 2 H) 7.25 (m, 1 H) 7.34 (m, 2 H) 7.42 (m, 2 H) 7.53 (d, J=9.15 Hz, 2 H) 8.33 (s, 1 H) 8.45 (d, J=8.29 Hz, 1 H) 9.26 (s, 1 H)

Ejemplo 55

N-benzil-1-metil-8-[4-(4-metil-4-oxidopiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida



A una solución de 39.4 mg (0.0774 mmol) de N-benzil-1-metil-8-{[4-(4-metilpiperazin-1-il)fenil]amino}-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida, se agregaron 17.4 mg (0.0774 mg) de ácido 3-clorobenzenocarboperoxoico y la mezcla se agitó a temperatura ambiente. Después de 45 minutos se agregó una solución acuosa de $NaHCO_3$ y el disolvente se removió. El tratamiento con metanol y la filtración

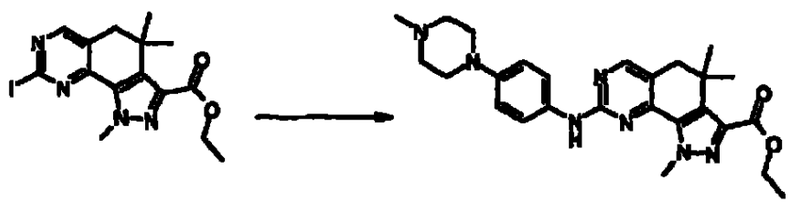
proporcionó 26.6 mg del compuesto del título (66 % de producto).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (t, J=7.74 Hz, 2 H) 3.00 (t, J=7.62 Hz, 2 H) 3.37 (m, 8 H) 3.15 (s, 3 H) 4.34 (s, 3 H) 4.43 (d, J=6.34 Hz, 2 H) 6.98 (d, J=9.15 Hz, 2 H) 7.24 (m, 1 H) 7.33 (m, 4 H) 7.57 (d, J=9.15 Hz, 2 H) 8.36 (s, 1 H) 8.70 (t, J=6.34 Hz, 1 H) 9.30 (s, 1 H).

Ejemplo 56

8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo

[B10-X00-M03(C01)-D01]



$Pd(OAc)_2$ (762.34 mg, 3.395 mmol), (±)-BINAP (2.145 g, 3.395 mmol) y dimetilformamida (250 mL) se cargaron en un frasco de fondo redondo lavado con argón. La mezcla se agitó bajo argón durante 30 minutos. Luego se agregaron 4-(4-metil-piperazin-1-il)-fenilamina (19.493 g, 101.908 mmol), 8-yodo-1,4,4-

trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo (14.00 g, 33.961 mmol), K_2CO_3 (60.00 g, 434.112 mmol) y dimetilformamida (250 mL). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y luego se calentó a 80°C en un baño de aceite bajo argón con buena agitación durante 3 horas.

Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró mediante filtración por succión lavandp con diclorometano y el filtrado se evaporó hasta secado. El crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 94:6) para producir 11.60 g (72% de producto) del compuesto del título puro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, J=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.71 (s, 2H) 3.03-3.15 (m, 4 H) 4.32 (q, J=7.07Hz, 2H) 4.33 (s, 3 H) 6.91 (d, J=9.02 Hz, 2 H) 7.53 (d, J=9.02 Hz, 2 H) 8.35 (s, 1 H) 9.28 (s, 1 H).

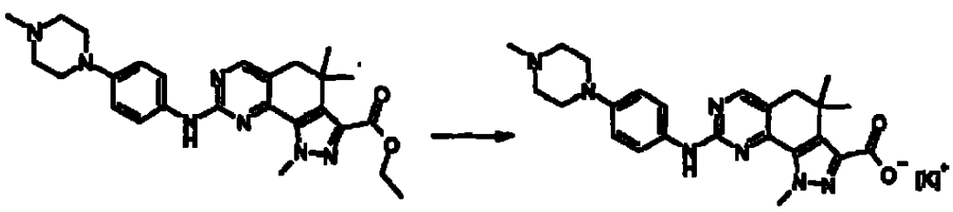
Al trabajar de acuerdo con el método anterior se preparó el siguiente compuesto:

Tabla XV

B19-X00-M03(C01)-D01	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (t, *J*=7.07 Hz, 3 H) 1.33 (s, 6 H) 2.71 (s, 2 H) 3.01 - 3.08 (m, 4 H) 3.70 - 3.80 (m, 4 H) 4.32 (q, *J*=7.07 Hz, 2 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.15 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 9.30 (s, 1 H)

Ejemplo 57

Sal de potasio de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B10-X00-M03(C01)-D02]



A una suspensión de 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo (11.60 g, 24.390 mmol) en etanol anhidro (450 mL), se agregó hidróxido de potasop al 1.5M en 95% etanol (63 mL) bajo buena agitación y la mezcla se calentó a reflujo durante 3 horas. Después de enfriamiento en un baño de hielo, se formó un sólido, que se filtró lavando con etanol, se secó a 40°C bajo vacío para producir 11.8 g (producción cuantitativa) del compuesto del título sólido blanco.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.58 (s, 2 H) 3.03-3.15 (m, 4 H) 4.17 (s, 3 H) 6.91 (d, J=9.02 Hz, 2 H) 7.54 (d, J=9.02 Hz, 2 H) 8.24 (s, 1 H) 9.12 (s, 1 H)

Al trabajar de acuerdo con el método anterior se prepararon los siguientes compuestos:

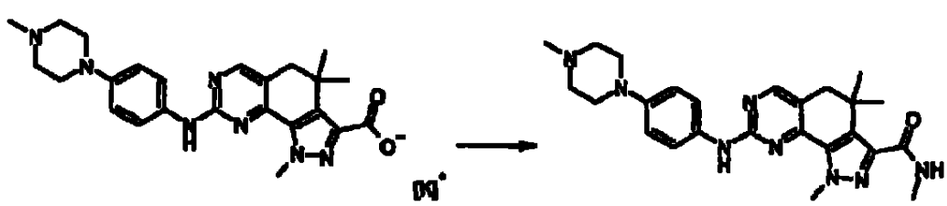
Tabla XVI

B04-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.73 (s, 2 H) 4.34 (s, 3 H) 6.98 (tt, *J* 7.36, 1.13, 1.10 Hz, 1 H) 7.31 (dd, *J* 8.47, 7.38 Hz, 2 H) 7.71 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.42 (s, 1 H) 9.53 (s, 1 H) 12.84 (s, 1 H)
B12-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.24 (s, 3 H) 2.45 (s, 4 H) 2.61 (s, 2 H) 2.84 (t, *J* 4.51 Hz, 4 H) 4.18 (s, 3 H) 7.52 (d, *J* 9.02 Hz, 1 H) 7.94 (dd, *J* 8.90, 2.44 Hz, 1 H) 8.09 (d, *J* 2.56 Hz, 1 H) 8.34 (s, 1 H) 9.63 (s, 1 H)
B13-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 2.25 (s, 3 H) 2.52 (m, 4 H) 2.61 (s, 2 H) 2.94 (t, *J* 4.51 Hz, 4 H) 4.20 (s, 3 H) 7.12 (d, *J* 8.90 Hz, 1 H) 7.53 (dd, *J* 8.78, 2.56 Hz, 1 H) 7.99 (d, *J* 2.56 Hz, 1 H) 8.31 (s, 1 H) 9.45 (s, 1 H)
B00-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.51 (s, 2 H) 4.16 (s, 3 H) 6.37 (s, 2 H) 8.07 (s, 1 H)
B19-X00-M03(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.58 (s, 2 H) 3.01 – 3.09 (m, 4 H) 3.71 – 3.79 (m, 4 H) 4.18 (s, 3 H) 6.91 (d, *J*=9.15 Hz, 2 H) 7.57 (d, *J*=9.15

	Hz, 2 H) 8.25 (s, 1 H) 9.14 (s, 1 H)
B109-X00-M00(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.48 (m, 4 H) 2.76 (t, *J*=7.68 Hz, 2 H) 2.96 (m, 6 H) 4.27 (s, 3 H) 6.99 (dd, *J*=10.00, 8.90 Hz, 1 H) 7.38 (ddd, *J*=8.87, 2.47, 0.85 Hz, 1 H) 7.68 (dd, *J*=15.49, 2.44 Hz, 1 H) 8.34 (s, 1 H) 9.45 (s, 1 H)
B13-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (s, 6 H) 2.25 (s, 3 H) 2.51 (m, 4 H) 2.91 (s, 2 H) 2.94 (t, *J* 4.39 Hz, 4 H) 4.25 (s, 3 H) 7.13 (d, *J* 8.78 Hz, 1 H) 7.53 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.00 (d, *J* 2.44 Hz, 1 H) 8.43 (s, 1 H) 9.49 (s, 1 H)
B12-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27 (s, 6 H) 2.24 (s, 3 H) 2.45 (s, 4 H) 2.84 (t, *J* 4.63 Hz, 4 H) 2.91 (s, 2 H) 4.23 (s, 3 H) 7.52 (d, *J* 8.78 Hz, 1 H) 7.93 (dd, *J* 8.78, 2.32 Hz, 1 H) 8.11 (d, *J* 2.56 Hz, 1 H) 8.44 (s, 1 H) 9.67 (s, 1 H)
B04-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.92 (s, 2 H) 4.37 (s, 3 H) 6.98 (tt, *J* 7.33, 1.10, 1.07 Hz, 1 H) 7.32 (dd, *J* 8.41, 7.44 Hz, 2 H) 7.72 (dd, *J* 8.66, 0.98 Hz, 2 H) 8.52 (s, 1 H) 9.56 (s, 1 H) 12.80 (s, 1 H)
B10-X00-M02(C01)-D02	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (s, 6 H) 2.23 (s, 3 H) 2.47 (m, 4 H) 2.89 (s, 2 H) 3.07 (m, 4 H) 4.21 (s, 3 H) 6.89 (d, *J*=9.17 Hz, 2 H) 7.54 (d, *J*=9.17 Hz, 2 H) 8.35 (s, 1 H) 9.14 (s, 1 H)

Ejemplo 58

Metilamida de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B10-X00-M03(C01)-D04]



A una suspensión de sal de potasio de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (9.5 g, 19.561 mmol) en una mezcla 1:1 de tetrahidrofurano anhidro y dimetilformamida (50 mL), se agregaron en este orden metilamina 2M en tetrahidrofurano (21.12 mL, 42.24 mmol), 1-hidroxibenzotriazol (5.332 g, 39. 458 mmol) y 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC) (7.567 g, 39.473 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas.

La mezcla de reacción se vertió en agua (2.5 L) y se extrajo con diclorometano (4 x 250 mL). Los extractos orgánicos combinados se lavaron con agua, se escicieron sobre sulfato de sodio anhidro, y el disolvente se removió bajo presión reducida. El crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: cloruro de metileno/metanol 94:6) para producir 8.20 g (92% de producto) del compuesto del título puro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.26 (s, 3 H) 2.44-2.54 (m, 4 H) 2.68 (s, 2 H) 2.76 (d, J=4.76 Hz, 3 H) 3.04-3.13 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, J=9.02 Hz, 2 H) 7.53 (d, J=9.02 Hz, 2 H) 8.15 (q, J=4.84 Hz, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)

Al trabajar de acuerdo con el método anterior se prepararon los siguientes compuestos:

Tabla XVII

B19-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.02 – 3.09 (m, 4 H) 3.72 – 3.79 (m, 4 H) 4.31 (s, 3 H) 6.93 (d, *J*=9.02 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)
B10-X00-M03(C01)-D25	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.28 (s, 3 H) 2.50 – 2.57 (m, 4 H) 2.70 (s, 2 H) 3.04 – 3.13 (m, 4 H) 4.26 (d, *J*=5.85 Hz, 2 H) 4.34 (s, 3 H) 6.92 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 8.94 (t, *J*=5.85 Hz, 1 H) 9.28 (s, 1 H)
B10-X00-M03(C01)-D30	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.28 (s, 3 H) 2.47 – 2.59 (m, 4 H) 2.69 (s, 2 H) 3.02 – 3.16 (m, 4 H) 3.83 (d, *J*=5.73 Hz, 2 H) 4.34 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.08 (s, 1 H) 7.36 (s, 1 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.12 (t, *J*=5.67 Hz, 1 H) 8.35 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M03(C01)-D162 Sal de tri clorhidrato	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.70 (s, 2 H) 2.85 (d, *J*=4.63 Hz, 3 H) 2.95 – 3.05 (m, 2 H) 3.11 – 3.25 (m, 2 H) 3.52 (d, *J*=11.46 Hz, 2 H) 3.67 (s, 3 H) 3.74 (d, *J*=13.66 Hz, 2 H) 4.00 (d, *J*=5.97 Hz, 2 H) 4.34 (s, 3 H) 6.99 (d, *J*=9.15 Hz, 2 H) 7.60 (d, *J*=9.02 Hz, 2 H) 8.37 (s, 1 H) 8.54 (t, *J*=6.04 Hz, 1 H) 9.39 (s, 1 H) 10.23 (s, 1 H)
B10-X00-M03(C01)-D20	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.36 (s, 6 H) 2.27 (s, 3 H) 2.50 – 2.57 (m, 4 H) 2.71 (s, 2 H) 3.07 – 3.13 (m, 4 H) 4.38 (s, 3 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.06 – 7.15 (m, 1 H) 7.31 – 7.40 (m, 2 H) 7.55 (d, *J*=9.15 Hz, 2 H) 7.80 (dd, *J*=8.54, 0.98 Hz, 2 H) 8.37 (s, 1 H) 9.29 (s, 1 H) 10.29 (s, 1 H)
B10-X00-M03(C01)-D09	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.70 (s, 2 H) 2.84 (d, *J*=4.15 Hz, 3 H) 3.03 (t, *J*=12.56 Hz, 2 H) 3.10 – 3.25 (m, 2 H) 3.36 – 3.55 (m, 2 H)

	3.74 (d, *J*=13.05 Hz, 2 H) 4.32 (s, 3 H) 4.45 (d, *J*=6.34 Hz, 2 H) 7.00 (d, *J*=9.02 Hz, 2 H) 7.21 – 7.29 (m, 1 H) 7.31 – 7.36 (m, 4 H) 7.59 (d, *J*=9.02 Hz, 2 H) 8.36 (s, 1 H) 8.77 (t, *J*=6.34 Hz, 1 H) 9.46 (s, 1 H) 10.46 (s, 1 H)
B10-X00-M03(C01)-D34	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (s, 3 H) 1.33 (s, 3 H) 2.27 (s, 3 H) 2.48 – 2.56 (m, 4 H) 2.67 (s, 2 H) 3.04 – 3.14 (m, 4 H) 3.71 (t, *J*=6.04 Hz, 2 H) 4.35 (s, 3 H) 4.96 (t, *J*=5.61 Hz, 1 H) 5.02 (dt, *J*=7.83, 6.20 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.22 – 7.28 (m, 1 H) 7.34 (t, *J*=7.44 Hz, 2 H) 7.38 – 7.42 (m, 2 H) 7.53 (d, *J*=9.15 Hz, 2 H) 8.34 (s, 1 H) 8.42 (d, *J*=8.17 Hz, 1 H) 9.26 (s, 1 H)
B10-X00-M03(C01)-D70	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.23 (s, 3 H) 1.36 (s, 3 H) 2.27 (s, 3 H) 2.45 - 2.54 (m, 4 H) 2.61 - 2.72 (m, 2 H) 3.07 - 3.12 (m, 4 H) 3.61 - 3.68 (m, *J*=12.44, 5.12 Hz, 1 H) 3.80 (dd, *J*=12.44, 9.51 Hz, 1 H) 4.35 (s, 3 H) 5.27 (td, *J*=9.21, 5.00 Hz, 1 H) 6.92 (d, *J*=9.15 Hz, 2 H) 7.27 - 7.33 (m, 1 H) 7.38 (t, *J*=7.44 Hz, 2 H) 7.48 (d, *J*=7.07 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.34 (s, 1 H) 8.93 (d, *J*=9.02 Hz, 1 H) 9.27 (s, 1 H)
B10-X00-M03(C01)-D163	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.08 (d, *J*=6.54 Hz, 3 H) 1.31 (s, 6 H) 2.17 (s, 6 H) 2.22 (s, 3 H) 2.45 (m, 6 H) 2.65 (s, 2 H) 3.04 (m, 4 H) 4.04 (m, 1 H) 4.29 (s, 3 H) 6.90 (d, *J*=9.02 Hz, 2 H) 7.49 (d, *J*=9.02 Hz, 2 H) 7.91 (d, *J*=8.46 Hz, 1 H) 8.32 (s, 1 H) 9.27 (s, 1 H)
B10-X00-M02(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.26 (s, 3 H) 2.47 (m, 4 H) 2.93 (s, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.32 Hz, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.53 (d, *J*=9.32 Hz, 2 H) 8.44 (s, 1 H) 9.28 (s, 1 H)

Adelante están reportados los datos de HPLC analítico/Masa para algunos compuestos representativos de la invención.

Tabla XVIII

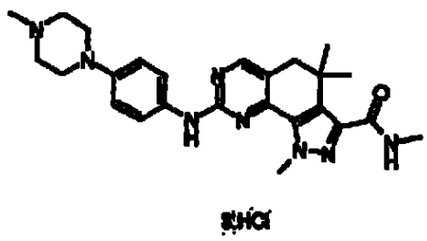
	M+H	Time 1	Method
B10-X00-M03(C01)-D136	560.34	2.2	1
B10-X00-M03(C01)-D26	532.34	2.25	1
B10-X00-M03(C01)-D86	518.33	2.43	1
B10-X00-M03(C01)-D137	534.32	2.34	1
B10-X00-M03(C01)-D116	556.36	2.45	1
B10-X00-M03(C01)-D79	535.31	2.5	1
B10-X00-M03(C01)-D123	517.3	2.67	1
B10-X00-M03(C01)-D135	517.3	2.64	1
B10-X00-M03(C01)-D138	505.3	2.63	1
B10-X00-M03(C01)-D139	506.29	2.45	1

B10-X00-M03(C01)-D95	521.29	2.77	1
B10-X00-M03(C01)-D119	521.29	2.77	1
B10-X00-M03(C01)-D81	558.36	2.6	1
B10-X00-M03(C01)-D115	544.34	2.45	1
B10-X00-M03(C01)-D105	531.31	2.9	1
B10-X00-M03(C01)-D140	545.33	2.87	1
B10-X00-M03(C01)-D100	545.33	3.05	1
B10-X00-M03(C01)-D82	505.3	3.1	1
B10-X00-M03(C01)-D97	505.3	3.19	1
B10-X00-M03(C01)-D121	572.34	3.23	1
B10-X00-M03(C01)-D06	491.28	2.93	1
B10-X00-M03(C01)-D104	505.3	3.21	1
B10-X00-M03(C01)-D113	531.31	3.07	1
B10-X00-M03(C01)-D83	549.29	3.45	1
B10-X00-M03(C01)-D131	519.31	3.47	1
B10-X00-M03(C01)-D102	475.29	3.54	1
B10-X00-M03(C01)-D122	545.33	3.32	1
B10-X00-M03(C01)-D85	506.29	3.24	3
B10-X00-M03(C01)-D93	559.34	3.61	1
B10-X00-M03(C01)-D94	493.28	3.58	1
B10-X00-M03(C01)-D60	567.31	3.92	1
B10-X00-M03(C01)-D117	533.33	3.77	1
B10-X00-M03(C01)-D34	567.31	3.99	1
B10-X00-M03(C01)-D87	567.31	4.21	1
B10-X00-M03(C01)-D108	634.35	4.07	1
B10-X00-M03(C01)-D91	533.29	4.01	1
B10-X00-M03(C01)-D114	602.35	4.1	1
B10-X00-M03(C01)-D14	515.32	4.84	1
B10-X00-M03(C01)-D141	552.31	4.34	1
B10-X00-M03(C01)-D109	580.34	4.89	1
B10-X00-M03(C01)-D107	531.28	3.56	1

Ejemplo 59

Sal de tri-clorhidrato de metilamida de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-

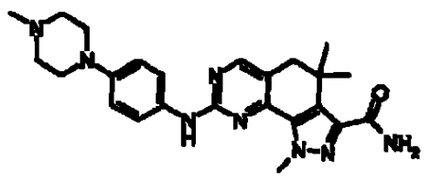
pirazolo[4,3-h]quinazolina-3-carboxílico [B10-X00-M03(C01)-D04]



Una metilamida de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (7.00 g, 15.192 mmol) disuelto en una mezcla 1:1 de metanol/diclorometano (149 mL) se agregó ácido clorhídrico 4M en dioxano (12.12 mL, 48.48 mL) y la solución se agitó a temperatura ambiente durante 2 horas. Después de remover el disolvente bajo presión reducida, el sólido rojizo se secó a 43°C bajo vacío durante 10 horas. Se obtuvieron 8.11 g del compuesto del título como un sólido rojo.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.69 (s, 2 H) 2.76 (d, J=4.76 Hz, 3 H) 2.85 (d, J=3.54 Hz, 3 H) 2.95-3.08 (m, 2 H) 3.10-3.26 (m, 2 H) 3.39-3.55 (m, 2 H) 3.74 (d, J=13.41 Hz, 2 H) 4.30 (s, 3 H) 7.00 (d, J=9.02 Hz, 2 H) 7.59 (d, J=8.90 Hz, 2 H) 8.16 (q, J=4.51 Hz, 1 H) 8.36 (s, 1 H) 9.44 (s, 1 H) 10.37 (s, 1 H)

Ejemplo 60



8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B10-X00-M03(C01)-D03]

A una suspensión de sal de potasio de ácido 8-[4-(4-metil-piperazin-1-il)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (185.5 mg, 0.382 mmol) en una mezcla 1:1 de tetrahidrofurano anhidro y dimetilformamida (4.8 mL), se agregaron en ese orden N-etildiisopropilamina (0.13 mL, 0.760 mmol), sal de amonio de 1-hidroxibenzotriazol (102 mg, 0.760 mmol). La mezcla de reacción se enfrió a 0°C, se trató con 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC) (146 mg, 0.760 mmol) y luego se agitó a temperatura ambiente durante 18 horas.

La mezcla de reacción se vertió en agua (10 mL) y el precipitado se filtró, se lavó con agua, se secó bajo vacío a

40°C durante 4 horas. Se obtuvieron 130 mg (76% de producto) del compuesto del título puro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.26 (s, 3 H) 2.46-2.56 (m, 4 H) 2.68 (s, 2 H) 3.04-3.14 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, J=9.15 Hz, 2 H) 7.29 (s, 1 H) 7.53 (d, J=9.15 Hz, 2 H) 7.55 (s, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)

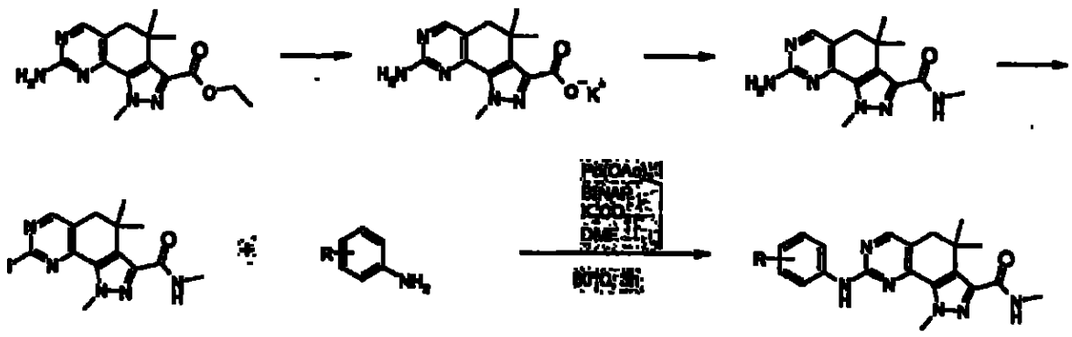
Al trabajar de acuerdo con el método anterior se prepararon los siguientes compuestos:

Tabla XIX

B04-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.71 (s, 2 H) 4.33 (s, 3 H) 6.97 (tt, *J* 7.38, 1.10 Hz, 1 H) 7.31 (m, 3 H) 7.56 (s, 1 H) 7.71 (dd, *J* 8.60, 1.04 Hz, 2 H) 8.41 (s, 1 H) 9.52 (s, 1 H)

B12-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.72 (s, 2 H) 2.87 (d, *J* 4.63 Hz, 3 H) 3.35 (m, 8 H) 4.34 (s, 3 H) 7.21 (d, *J* 8.78 Hz, 1 H) 7.32 (s, 1 H) 7.56 (s, 1 H) 7.59 (dd, *J* 8.78, 2.56 Hz, 1 H) 8.01 (d, *J* 2.44 Hz, 1 H) 8.43 (s, 1 H) 9.68 (s, 1 H) 10.39 (s, 1 H)
B13-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.73 (s, 2 H) 2.88 (d, *J* 4.63 Hz, 3 H) 3.32 (m, 8 H) 4.32 (s, 3 H) 7.33 (s, 1 H) 7.54 (d, *J* 8.90 Hz, 1 H) 7.56 (s, 1 H) 8.01 (dd, *J* 8.72, 2.38 Hz, 1 H) 8.12 (d, *J* 2.56 Hz, 1 H) 8.45 (s, 1 H) 9.86 (s, 1 H) 10.35 (s, 1 H)
B19-X00-M03(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.68 (s, 2 H) 3.00 – 3.13 (m, 4 H) 3.70 – 3.80 (m, 4 H) 4.31 (s, 3 H) 6.92 (d, *J*=9.02 Hz, 2 H) 7.29 (s, 1 H) 7.51 – 7.59 (m, 3 H) 8.34 (s, 1 H) 9.27 (s, 1 H)
B13-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.29 (m, 6 H) 2.86 (d, *J* 4.39 Hz, 3 H) 2.95 (s, 2 H) 3.34 (m, 8 H) 4.37 (s, 3 H) 7.21 (d, *J* 8.78 Hz, 1 H) 7.29 (s, 1 H) 7.45 (s, 1 H) 7.58 (dd, *J* 8.84, 2.50 Hz, 1 H) 8.04 (d, *J* 2.44 Hz, 1 H) 8.53 (s, 1 H) 9.71 (s, 1 H) 10.49 (s, 1 H)
B12-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (m, 6 H) 2.88 (d, *J* 4.39 Hz, 3 H) 2.96 (s, 2 H) 3.38 (m, 8 H) 4.35 (s, 3 H) 7.29 (s, 1 H) 7.46 (s, 1 H) 7.54 (d, *J* 8.90 Hz, 1 H) 8.00 (dd, *J* 8.66, 2.32 Hz, 1 H) 8.15 (d, *J* 2.44 Hz, 1 H) 8.55 (s, 1 H) 9.89 (s, 1 H) 10.32 (s, 1 H)
B04-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (s, 6 H) 2.95 (s, 2 H) 4.35 (s, 3 H) 6.98 (tt, *J* 7.35, 1.04, 0.98 Hz, 1 H) 7.27 (s, 1 H) 7.31 (dd, *J* 8.35, 7.50 Hz, 2 H) 7.47 (s, 1 H) 7.72 (dd, *J* 8.54, 0.98 Hz, 2 H) 8.51 (s, 1 H) 9.55 (s, 1 H)
B10-X00-M02(C01)-D03	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.26 (s, 3 H) 2.47 (m, 4 H) 2.93 (s, 2 H) 3.09 (m, 4 H) 4.33 (s, 3 H) 6.93 (d, *J*=9.32 Hz, 2 H) 7.25 (s, 1 H) 7.46 (s, 1 H) 7.53 (d, *J*=9.32 Hz, 2 H) 8.44 (s, 1 H) 9.28 (s, 1 H)

Ejemplo 61



Etapa 1. Sal de potasio de ácido 8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B00-X00-M03(C01)-D02]

Una suspensión de 8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato de etilo (20.00 g, 66.368 mmol) en etanol anhidro (250 mL), se agregó hidróxido de potasio 1.5M en etanol (150 mL) bajo buena agitación y la mezcla se calentó a reflujo durante 1.5 horas. Después de enfriar en un baño de hielo, se formó un sólido; que se filtró lavando con etanol, se secó a 40°C bajo vacío para producir 17.34 g (84% de producto) de compuesto sólido blanco.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (s, 6 H) 2.51 (s, 2 H) 4.16 (s, 3 H) 6.37 (s, 2 H) 8.07 (s, 1 H)

Etapa 2. Metalamida de ácido 8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B00-X00-M03(C01)-D04]

A una suspensión de sal de potasio de ácido 8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (17.00 g, 54.594 mmol) en una mezcla 1:1 de tetrahidrofurano anhidro y dimetilformamida (340 mL), se agregaron en ese orden metilamina 2M en tetrahidrofurano (40.80 mL, 81.60 mmol), 1-hidroxibenzotriazol (8.840 g, 65.418 mmol) y 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC) (12.540 g, 65.418 mmol), y la suspensión espesa se agitó a temperatura ambiente durante 20 horas.

La mezcla de reacción se vertió en agua (2.5 L) y se extrajo con diclorometano (4 x 250 mL). Los extractos orgánicos combinados se lavaron con agua (50 mL), se secaron sobre sulfato de sodio anhidro, y el disolvente se removió bajo presión reducida. Se obtuvieron 17.0 g de sólido amarillento que se trituraron con dietiléter para producir 13.05 g (87% de producto) del compuesto deseado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.60 (s, 2 H) 2.75 (d, J=4.76 Hz, 3 H) 4.30 (s, 3 H) 6.55 (s, 2 H) 8.12 (q, J=4.39 Hz, 1 H) 8.17 (s, 1 H).

Al trabajar de una manera análoga se prepararon los siguientes compuestos:

Metilamida de ácido 8-amino-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B00-X00-M00(C01)-D04]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.69-2.74 (m, 2 H) 2.74 (d, J=4.76 Hz, 3 H) 2.94 (t, J=7.56 Hz, 2 H) 4.31 (s, 3 H) 6.54 (s, 2 H) 7.99-8.08 (m, 1 H) 8.18 (s, 1 H);

8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxamida [B00-X00-M03(C01)-D03]

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 6 H) 2.61 (s, 2 H) 4.30 (s, 3 H) 6.57 (s, 2 H) 7.27 (s, 1 H) 7.51 (s, 1 H) 8.17 (s, 1 H)

Etapa 3. Metilamida de ácido 8-yodo-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico

En un frasco de fondo redondo mantenido bajo atmósfera de argón, se disolvió metilamida de ácido de etil 8-amino-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (13.00 g, 45.400 mmol) en dimetoxietano anhidro

(800 mL); se agregaron en ese orden yoduro de cesio (11.795 g, 45.400 mmol), yoduro bisublimado (5.761 g, 22.698 mmol), yoduro de cobre (I) (2.594 g, 13.621 mmol), y nitrito de *iso*-amilo (9.107 mL, 68.100 mmol) y la mezcla se calentó a 70°C durante 22 horas.

Después de enfriar a temperatura ambiente, los materiales sólidos se removieron mediante filtración por succión, lavando con diclorometano. El filtrado se concentró a 400 mL, se diluyó con diclorometano (1000 mL), se lavó con hidróxido de amonio al 30% (100 mL), tiosulfato de sodio al 5% (50 mL), agua (4 x 100 mL), y se secó sobre sulfato de sodio anhidro. El disolvente se removió bajo vacío para producir 11.00 g de aceite oscuro que se trituró con dietiléter para producir 4.300 g del compuesto del título como un sólido amarillo. La purificación de las aguas madre mediante cromatografía flash sobre gel de sílice (eluente diclorometano/metanol 97:3) produjo 2.04 g adicionales de compuesto sólido amarillento (35% de producto en general).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.76 (d, J=4.76 Hz, 3 H) 2.80 (s, 2 H) 4.24 (s, 3 H) 8.16-8.25 (m, 1 H) 8.48 (s, 1 H)

Etapa 4. Metilamida de ácido 8-[3-(4-metil-piperazin-1-ilmetil)-fenilamino]-1,4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico [B104-X00-M03 (C01)-D04]

$Pd(OAc)_2$ (16.34 mg, 0.0728 mmol), (±)-BINAP (45.33 mg, 0.0728 mmol) y dimetilformamida (12 mL) se cargaron en un frasco de fondo redondo lavado con argón. La mezcla se agitó bajo argón durante 30 minutos. Luego se agregaron 3-(4-metil-piperazin-1-ilmetil)-fenilamina (448.4 mg, 2.184 mmol), metilamida de ácido de etil 8-yodo-1, 4,4-trimetil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxílico (300 mg, 0.728 mmol), K_2CO_3 (1.508 g, 10.910 mmol) y dimetilformamida (10 mL). La mezcla resultante se calentó a 80°C en un baño de aceite bajo argón con buena agitación durante 3 horas.

Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró mediante filtración por succión lavando con diclorometano y el filtrado se evaporó hasta secado. El crudo se purificó mediante cromatografía flash sobre gel de sílice (eluente: diclorometano/metanol 95:5) para producir 215 mg (62% de producto) del compuesto del título puro.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 6 H) 2.25 (s, 3 H) 2.42 (m, 4 H) 2.71 (s, 2 H) 2.77 (d, J=4.76 Hz, 3 H) 3.44 (m,

4 H) 3.48 (s, 2 H) 4.35 (s, 3 H) 6.91 (d, J=7.31 Hz, 1 H) 7.26 (t, J=7.68 Hz, 1 H) 7.56 (d, J=8.78 Hz, 1 H) 7.76 (s, 1 H) 8.15 (s, 1 H) 8.41 (s, 1 H) 9.5 (s, 1 H)

Al trabajar de acuerdo con el método anterior se prepararon los siguientes compuestos:

Tabla XX

B10-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.26 (s, 3 H) 2.44 - 2.54 (m, 4 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.04 - 3.13 (m, 4 H) 4.31 (s, 3 H) 6.91 (d, *J*=9.02 Hz, 2 H) 7.53 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.84 Hz, 1 H) 8.34 (s, 1 H) 9.25 (s, 1 H)
B09-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.27 (s, 3 H) 2.52 (m, 4 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.13 (m, 4 H) 4.33 (s, 3 H) 6.59 (d, *J*=7.31 Hz, 1 H) 7.14 (t, *J*=7.68 Hz, 1 H) 7.23 (s, 1 H) 7.26 (d, *J*=8.78 Hz, 1 H) 8.15 (s, 1 H) 8.39 (s, 1 H) 9.33 (s, 1 H)
B101-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.55 - 3.62 (m, 13 H) 2.71 (s, 2 H) 2.75 - 2.79 (m, *J*=4.76 Hz, 3 H) 4.33 (s, 3 H) 7.25 (d, *J*=10.24 Hz, 2 H) 7.69 (d, *J*=7.80 Hz, 2 H) 8.10 - 8.18 (m, 1 H) 8.41 (s, 1 H) 9.55 (s, 1 H)
B19-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.02 - 3.09 (m, 4 H) 3.72 - 3.79 (m, 4 H) 4.31 (s, 3 H) 6.93 (d, *J*=9.02 Hz, 2 H) 7.55 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)

	M+H	RT	método
B121-X00-M03(C01)-D04	442.514	4.40	1
B122-X00-M03(C01)-D04	393.461	4.70	1
B123-X00-M03(C01)-D04	380.422	3.42	1

B107-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.06 - 3.13 (m, 4 H) 3.73 - 3.78 (m, 4 H) 4.33 (s, 3 H) 6.59 (dd, *J*=7.93, 2.07 Hz, 1 H) 7.16 (t, *J*=8.11 Hz, 1 H) 7.23 (t, *J*=2.01 Hz, 1 H) 7.30 (dd, *J*=7.74, 1.40 Hz, 1 H) 8.16 (q, *J*=4.59 Hz, 1 H) 8.39 (s, 1 H) 9.35 (s, 1 H)
B102-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 2.35 (s, 4 H) 2.70 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 3.43 (s, 2 H) 3.58 (s, 4 H) 4.33 (s, 3 H) 7.25 (s, 2 H) 7.66 (s, 2 H) 8.40 (s, 1 H) 9.51 (s, 1 H)
B105-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.35 (s, 7 H) 2.38 (s, 4 H) 2.71 (s, 2 H) 2.77 (d, *J*=4.76 Hz, 3 H) 3.44 (s, 2 H) 3.58 (s, 5 H) 4.36 (s, 3 H) 6.87 - 6.99 (m, 1 H) 7.25 (t, *J*=7.56 Hz, 1 H) 7.58 (d, *J*=6.71 Hz, 1 H) 7.76 (s, 1 H) 8.41 (s, 1 H)
B103-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 (s, 6 H) 1.64 - 2.07 (m, 4 H) 2.37 - 2.62 (m, 5 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.63 Hz, 3 H) 2.81 - 3.00 (m, 2 H) 4.30 (s, 3 H) 4.34 - 4.46 (m, 1 H) 6.94 (d, *J*=9.02 Hz, 2 H) 7.58 (d, *J*=9.02 Hz, 2 H) 8.15 (q, *J*=4.55 Hz, 1 H) 8.36 (s, 1 H) 9.34 (s, 1 H)
B106-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.34 (s, 6 H) 1.70 - 2.18 (m, 4 H) 2.59 (s, 3 H) 2.71 (s, 2 H) 2.77 (d, *J*=4.76 Hz, 3 H) 2.93 - 3.50 (m, 4 H) 4.35 (s, 3 H) 4.40 - 4.57 (m, 1 H) 6.61 (dd, *J*=7.93, 2.07 Hz, 1 H) 7.21 (t, *J*=8.11 Hz, 1 H) 7.26 - 7.32 (m, 1 H) 7.47 (s, 1 H) 8.12 - 8.19 (m, 1 H) 8.42 (s, 1 H) 9.51 (s, 1 H)
B120-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 - 1.24 (m, 6 H) 1.33 (s, 6 H) 2.68 (s, 2 H) 2.76 (d, *J*=4.76 Hz, 3 H) 2.79 - 3.52 (m, 9 H) 4.31 (s, 3 H) 6.94 (d, *J*=8.78 Hz, 2 H) 7.55 (d, *J*=8.78 Hz, 2 H) 8.15 (q, *J*=4.63 Hz, 1 H) 8.34 (s, 1 H) 9.28 (s, 1 H)
B173-X00-M03(C01)-D04	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 (s, 6 H) 2.40 – 2.50 (m, 4 H) 2.68 (s, 2 H) 2.74 (d, *J*=4.76 Hz, 3 H) 3.53 (s, 2 H) 3.60 (m, 4 H) 4.30 (s, 3 H) 6.98 (d, 1 H) 7.06 (dd, 1 H) 7.23 (d, 1 H) 8.14 (q, 1 H) 8.37 (s, 1 H) 9.39 (s, 1 H) 10 (bs, 1 H)

Adelante están reportados los datos de HPLC analítico/Masa para algunos compuestos representativos de la invención

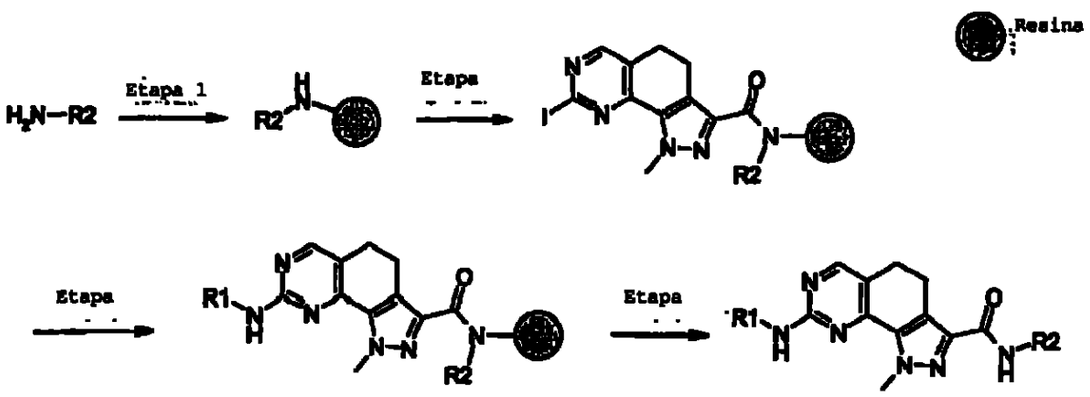
Tabla XXI

B124-X00-M03(C01)-D04	379.434	4.86	1
B125-X00-M03(C01)-D04	406.503	5.60	1
B126-X00-M03(C01)-D04	395.433	4.37	1
B127-X00-M03(C01)-D04	442.514	4.90	1
B128-X00-M03(C01)-D04	406.46	5.40	1
B114-X00-M03(C01)-D04	393.461	4.35	1
B129-X00-M03(C01)-D04	406.46	4.10	1
B11-X00-M03(C01)-D04	393.461	4.50	1
B130-X00-M03(C01)-D04	406.46	4.10	1
B131-X00-M03(C01)-D04	449.524	6.10	1
B168-X00-M03(C01)-D04	420.487	4.50	1
B132-X00-M03(C01)-D04	448.54	6.14	1
B133-X00-M03(C01)-D04	412.488	4.90	1
B134-X00-M03(C01)-D04	407.487	4.90	1
B135-X00-M03(C01)-D04	406.46	4.80	1
B21-X00-M03(C01)-D04	429.498	4.66	1
B136-X00-M03(C01)-D04	439.489	4.76	1
B137-X00-M03(C01)-D04	409.46	4.7	1
B138-X00-M03(C01)-D04	393.461	5.02	1
B139-X00-M03(C01)-D04	407.487	4.77	1
B140-X00-M03(C01)-D04	393.46	4.62	1
B141-X00-M03(C01)-D04	407.487	4.60	1
B142-X00-M03(C01)-D04	395.433	4.05	1
B143-X00-M03(C01)-D04	406.503	6.10	1
B144-X00-M03(C01)-D04	446.568	6.27	1
B145-X00-M03(C01)-D04	420.53	3.41	1
B17-X00-M03(C01)-D04	434.557	5.27	1
B146-X00-M03(C01)-D04	488.648	4.6	1
B147-X00-M03(C01)-D04	420.53	3.58	1
B148-X00-M03(C01)-D04	407.487	4.33	1
B149-X00-M03(C01)-D04	407.487	4.50	1
B150-X00-M03(C01)-D04	492.549	3.85	1
B151-X00-M03(C01)-D04	486.566	5.38	1
B152-X00-M03(C01)-D04	510.632	6.60	1
B153-X00-M03(C01)-D04	512.604	5.55	1
B154-X00-M03(C01)-D04	506.576	5.34	1
B155-X00-M03(C01)-D04	504.604	5.03	1
B156-X00-M03(C01)-D04	489.593	4.45	1
B13-X00-M03(C01)-D04	496.028	4.28	1
B117-X00-M03(C01)-D04	540.479	4.38	1
B157-X00-M03(C01)-D04	512.604	6.60	1
B158-X00-M03(C01)-D04	466.53	5.73	1
B159-X00-M03(C01)-D04	510.632	4.94	1
B160-X00-M03(C01)-D04	491.609	3.71	1
B161-X00-M03(C01)-D04	490.577	5.41	1
B162-X00-M03(C01)-D04	448.584	3.96	1
B163-X00-M03(C01)-D04	476.594	3.82	1
B164-X00-M03(C01)-D04	434.557	3.69	1
B165-X00-M03(C01)-D04	436.486	4.44	1
B109-X00-M03(C01)-D04	479.573	3.93	1

560

B168-X00-M03(C01)-D04	483.545	5.07	1
B12-X00-M03(C01)-D04	529.58	4.66	1
B167-X00-M03(C01)-D04	505.635	3.75	1

Ejemplo 62



Etapa 1. Cargas las aminas primarias sobre un soporte sólido (resina)

A: Caso en donde la "resina" es polietlenglicol injertado con aminometilpoliestireno- de 4-(4-formil-3-metoxifenoxi)butirilo al 1% DVB:

Para cada variante de la amina primaria R2, 1 gramo (0.39 mmol) de la resina anteriormente citada fue cargada a un tubo de reacción Argonaut Queso 210 de 10 mL. Se agregó ortoformato de trimetilo (7 mL9 al tuno junto con 5 equivalentes (1.95 mmol) de cada amina primaria (indicadas

como R2 en el esquema). La reacción fue mezclada en el Queso a 25° C durante 16 horas seguido por unperiodo de 2 horas de calentamiento a 70° C. Después de enfriar y remover la solución de reacción, la resina fuje lavada una vez con ortoformato de trimetilo (7 mL cada uno) y tres veces con metanol anhidro (7 mL). El metanol anhidro (5 mL) fue entonces agregado a la resina, seguido por la adición de 148 mg (3.9 mmol, 10 equivalentes) de borohidruro de sodio. Después de que una evolución de gas vigorosa cesó, el tubo fue tapado y mezclado durante 8 horas a temperatura ambiente. La resina fue lavada 3 veces con metanol (5 mL), tres veces con metanol/agua (1:1, 5 mL), y tres veces con DMF (5 mL). La resina fue entonces tratada con 20% de piperidina en DMF durante 1 hora a temperatura ambiente. Nuevamente, la resina fue lavada tres veces con DMF (5 mL), tres veces con metanol (5 mL), y tres veces con diclorometano (5 mL). Una muestra de resina fue ensayada en cuanto a la carga cuantitativa de amina usando el método Fmoc UV-espectrométrico descrito adelante. Cualitativamente, la resina fue analizada usando el método de ensayo cloranil descrito más abajo.

B: Caso en donde la "resina" es amida Rink, 4-(2',4'-dimetoxifenil-fmoc-aminometil)fenoxi (copoliestireno-1% DVB):

1 g (0.39 mmol) de la resina anteriormente mencionada fue cargada en un tubo de reacción Argonaut Queso 210 de 10 mL. La resina fue tratada con 20% de piperidina en DMF durante 5 minutos y entonces un segundo tratamiento ocurrió durante minutos a temperatura ambiente. La resina fue lavada con DMF (3 x 5 mL), con metanol (3 x 5 mL) y diclorometano (3 x 5 mL).

La carga de amina cuantitativa usando el me´todo Fmoc UV-espectrométrico:

Una cantidad parada precisamente (25 mg ± 5 mg) de resina cargada seca, fue cargada en una jeringa de polipropileno de 3 mL, ajustada con un disco de filtro. A la jeringa, se disolvieron 3 equivalentes de cloroformato de 9-fluorenilmetilo en 1 mL de diclorometano que fueron cargados y 1.5 equivalentes de N,N-diisopropiletilamina fueron agregados entonces. La resina fue agitada por medio de un agitador orbital, durante 1 hora. La resina fue lavada con DMF (3 x 2 mL, 5 min), con metanol (3 x 2 mL, 5 min), y con DCM (3 x 2 mL, 5 min).

1 mL de una solución al 20% de piperidina en DMF fue retirada de la jeringa y agitada durante 5 minutos a temperatura ambiente. La solución fue dispensada en un frasco volumétrico

de 10 mL. Una segunda alícuota de la solución de piperidina al 20% en DMF fue retirada y agitada durante 30 minutos a temperatura ambiente. Nuevamente, la solución fue dispensada dentro del mismo frasco volumétrico de 10 mL (solución de partida). Se agregó DMF al frasco volumétrico para lograr un volumen total de 10 mL. Este frasco volumétrico que contenía la solución de partida fue agitado fuertemente y exactamente 0.5 mL fueron transferidos a un segundo frasco volumétrico de 10 mL (solución de ensayo). Nuevamente, se agregó DMF al frasco volumétrico hasta el volumen total de 10 mL. La absorbancia de esta solución de ensayo fue medida a través de un espectrómetro UV-Vis *Amerasham Pharmacia Biotech Ultrospec 3000 Pro,* a λ=302 nm contra DMF como blanco. La post reacción de la sustitución de la resina fue calculada usando la siguiente fórmula:

$$Carga\ (mmol/g) = (A_{302}\ X\ 20\ veces\ X\ 10\ mL)/8100\ X\ wt$$

En donde A_{302} es la absorbancia UV en λ=302 nm, ε=8100 es elcoeficiente de extinción del aducto piperidina-fluorenona y *wt* es la tara de la resina en miligramos.

El ensayo cualitativo de cloranil (3,4,5,6-tetracloro-1,2-benzoquinona) para la resina ligó las aminas secundarias. Una pequeña alícuota de resina pre-lavada que contenía la amina

sujeta fue colocada en un tubo de micro-ensayo. Los granos fueron lavados una vez con acetona y el disolvente fue removido por decantación. Una gota de la solución de ensayo de cloranil fue agregada al tubo de ensayo y se le permitió permanecer a temperatura ambiente durante 5 minutos. Un color verde oscuro a café fue una indicación positiva de una amina secundaria. La intensidad del color fue una indicación no cuantitativa de la concentración de la amina secundaria.

Solución de ensayo: una solución saturada de 3,4,5,6-tetracloro-1,2-benzoquinona en tolueno a temperatura ambiente.

Etapa 2. Acilación del sólido que soporta la amina con fluoruro de 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carbonilo

Para cada variante de amina primaria R2 cargada en 1 g (0,30 mmol) de la resina en la etapa 1 anterior, el siguiente reactivo de fluoruro de ácido carboxílico pre-activado fue agregado. En 5 mL de diclorometano, se disolvieron 166 mg (0.47 mmol, 1.2 equivalentes) de 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]quinazolina-3-carboxilato, 155 mg (0.585 mmol, 1.5 equivalentes) de hexafluorofosfato de tetrametilfluoroformamidinio y 0.102 mL (0.585 mmol, 1.5

equivalentes) de N,N-diisopropiletilamina. Se agregó gota a gota N,N-dimetilacetamida a la solución hasta que todos los reactivos estaban en la solución con sonicación. El sistema de reacción fue agitado a temperatura ambiente durante 30 minutos. Se agregó 0.102 mL (0.585 mmol, 1.5 equivalentes) de N,N-diisopropiletilamina adicional a la solución, en 30 minutos, y el contenido completo fue cargado a la resina en el sintetizador Queso 210. La resina fue mezclada durante 18 horas a temperatura ambiente. La resina fue drenada del cóctel de acilación y lavada con DMF (3 x 5 mL, 5 minutos), con metanol (3 x 5 mL, 5 minutos), y con DCM (3 x 5 mL, 5 minutos). La resina fue secada a partir de DCM bajo vacío. La resina fue ensayada cualitativamente para el completamiento de la reacción de acilación usando el método de ensayo de cloranil. Una muestra de cada resina seca fue sometida a un análisis cuantitativo Fmoc UV-espectrométrico para determinar el grado de acilación de enlace de resina.

Etapa 3. Afinación catalítica del sólido soportado 8-yodo-1-metil-4,5-dihidro-1H-pirazolo[4,3-h]qunazolina-3-carboxamida

Usando un cassette sintetizador Argonaut Trident de 4 mL, se cargaron 200 mg (0.078 mmol) de cada tipo de resina de la etapa 2 anterior en frascos separados. A cada uno de los frascos del reactor lavados con argón, se agregó carbonato de

potasio (0,158 g, 1.56 mmol), acetato de paladio [$Pd(Oac)_2$] (1.8 mg, 0.008 mmol, 10%), (±)-BINAP (5.0 mg, 0.008 mmol, 10%) y la amina R1 correspondiente (0.156 mmol, 2 equivalentes) en dimetilacetamida (2 mL). La mezcla resultante fue agitada a temperatura ambiente durante 1 hora y luego se calentó a 60° C durante 16 horas sobre la estación de síntesis de la Unidad Térmica de Agitación Externa Argonaut Trident (EATU).

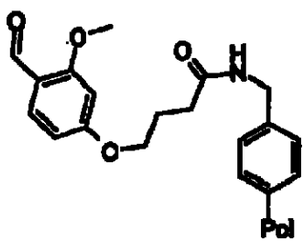
La resina fue drenada del cóctel de síntesis y lavada usando la estación de síntesis Argonaut Trident EATU con DMF (1 x 2 mL, 5 min), con agua (1 x 2 mL, 5 min), con DMF/agua (1:1) (3 x 2 mL, 5 min), con DMF (3 x 2 mL, 5 min), con metanol (3 x 2 mL, 5 min) y con DCM (3 x 2 mL, 5 min).

Etapa. 4 Ruptura del 8-amino-1-metil-4, 5-dihidro-1H-pirazolo [4,3-h] quinazolina-3-carboxamida diferencialmente sustituida del soporte sólido.

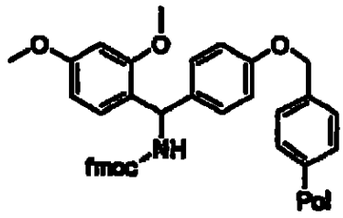
A cada frasco reactor Argonaut Trident 2 mL del siguiente cocktail de ruptura de resina fueron agregados: diclorometano (50 mL), acido trifluoroacético (49 mL) y agua (1 mL).

La resina suspendida en el cóctel de ruptura fue agitada durante 1 hora a temperatura ambienten el la estación de

síntesis Argonaut Trident EATU. La solución contenida que contenía los productos crudos fue capturada en frascos separados con tres resinas adicionales lavando con diclorometano (2 mL cada una) fueron también capturadas en los mismos frascos correspondientes.



4-(4-formil-3metoxifenoxi)butirilo aminometil) polietileno glycol insertado con Aminometilpoliestireno-1% DVB



4-(2',4'-dimetoxifenil-fmoc-fenoxi(copoliestireno-1%DVB)

EJEMPLO 63

N- [3-cloro-4- (4-metilpiperazin-1-il) fenil] guanidina

ETAPA 1.1, 3-bis (terc-butoxicarbonil) guanidina



15g of 1, 3-bis (terc-butoxicarbonil)-2-metil-2-tiopseudourea (0.052 mol) fueron suspendidos en 150 mL de amoniaco gaseoso en metanol y la mezcla fue agitada a temperatura ambiente en

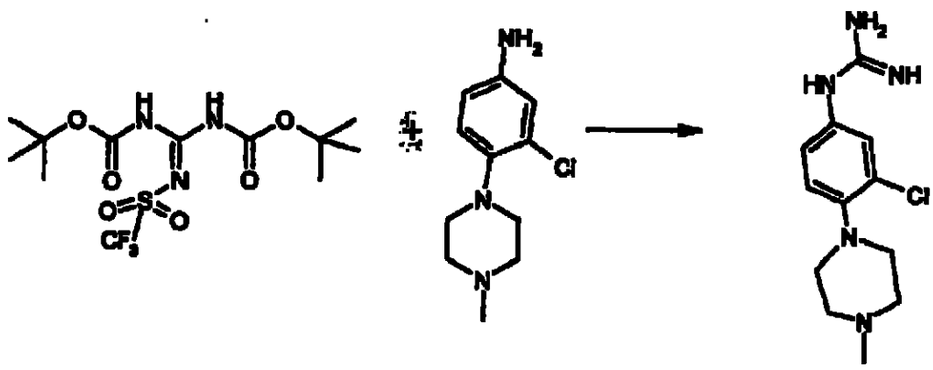
una botella cerrada a temperatura ambiente. La solución resultante fue concentrada en vacío hasta que 10 g (74% de producto) del compuesto titulado precipitado tiempo recolectado por filtración

ETAPA2 1,3-bis (terc-butoxicarbonil)-2-trifluorometanosulfonilguanidina



una solución de 5.2 g (20 mmol) de 1,3-bis (terc-butoxicarbonil) guanidina en 100 mL de diclorometano seco fue enfriada a -78°C bajo agitació y se agrego gota a gota 5.6 g (20 mmol) de anhidruro trifluorometanosulfónico. La mezcla de reacción se le permitió estar a temperatura ambiente y se agito durante 5 horas. Una solución acuosa de $NaHSO_4$ fue agregada y la capa orgánica fue sacada sobre Na_2SO_4 y evaporada hasta secado. El residuo fue purificado por cromatografía sobre columna de gel de sílice (eluente eter petróleo / acetato de etilo 7/3) para dar 4.0 g (51% de producto) del compuesto titulado.

ETAPA3.N-[3-cloro-4-(4-metilpiperazin-1-il) fenil] guanidina

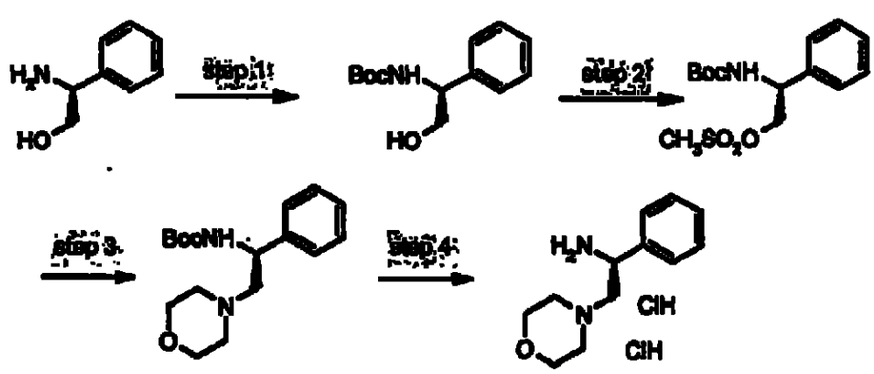


A una solución de 3.0 g (13.3 mmol) de 4- (3-cloro-4-metilpiperazin-1-il) anilina y 2.22 mL (16.0 mmol) de trietilamina en 36 mL de diclorometano, 6.0 g (15.3 mmol) de 1,3-bis(terc-butoxicarbonil)2-trifluorometanosulfonilguanidina fueron agregados. La mezcla de reacción fue agitada a temperatura ambiente durante 72 horas. La solución fue diluida con diclorometano adicional, lavada con agua y el disolvente secado con Na_2SO_4 y evaporado al vacío. El residuo fue purificado por cromatografía sobre una columna de gel de sílice (eluente diclorometano/metanol 92/8) dando 5.4 g (86.2% de producto) de un intermedio protegido, que fue tratado con 60 mL de HCl 4-N en dioxano. La mezcla fue agitada a temperatura ambiente durante la noche. El disolvente fue removido bajo presión reducida, el residuo fue redisuelto en agua, la solución resultante fue neutralizada y el producto extraído con acetato de etilo. El disolvente fue removido bajo presión reducida para dar 2.4 g (78.7% de producto) del compuesto titulado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 2.48 (m, 4 H) 2.90 (m, 4 H) 5.38 (bs, 4 H) 6.72 (dd, J2.44,8.42 Hz, 1 H) 6.82 (d, J2. 44,1 H) 7.01 (d, J8.42 Hz, 1 H).

Por medio de trabajar de manera análoga, peo empleando el derivado de anilina, sustituid adecuado ,los siguientes compuestos fueron preparados: N- [3- (4-metilpiperazin-1-il) fenil]guanidina;N-[4-(4-metilpiperazin-1-il)fenil] guanidina ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (s, 3 H) 7.09 (m. 4 E 7. 41 (s, 2 H) 9.85(s, 1 H) 11.39 (s, 1 H) (como dichicloruros) ; N- [4- (4-metilpiperazin-1-il)-3-(trifluorometil) fenil] guanidina ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.43 (m, 4 H) 2.80 (m, 4 H) 5.46 (bs, 4 H) 7.02 (m, 2 H) 7. 37 (d, 1 H, J 8.42 Hz); N- (3-clorofenil) guanidina.

Example 64



ETAPA1. Terc-butil (1S)-2-hydroxi-1-feniletilcarbamato de fenil-letil

Una solución de 40 g (0. 291 mol) de (2S) -2-amino-2-feniletanol en 1250 mL de etilacetato y 99.83 mL (0. 583 mol) de N-etil-N,-diisopropilamina fue enfriada 0°C y se agrego por porciones 76.21 g (0.349 mol) de dicarbonato de di-terc-butilo. La mezcla fue agitada a temperatura ambiente durante 3 horas y luego esta fue lavada con 400 mL de $KHSO_4$ 1m.La capa orgánica fue secada Na_2SO_4 proporcionando así 69.88 g del compuesto titulado.

ETAPA2.

metanosulfoato(2S)-2-[(terc-butoxicarbonil)amino-2-feniletilo

La solución de 68.9 g (0.29 mol) de (1S)-2-hidroxi-1-feniletilcarbamato de eter butilo y trietilamina (40.36 mL, 0.29 mol) en 700 mL de diclorometano seco bajo atmósfera inerte fueron enfriados a -10°C y se agrego gota a gota 24.79 mL (0.319 mol) de cloruro de metilo. Después de 2 horas a 0°C la mezcla fue vertida en hielo y agua y extraída con diclorometano. La fase orgánica fue lavada con HCl, diluido, $NaHCO_3$, acuoso solución salina y secado sobre Na_2SO_4 produciendo 89.8 g de producto (98 %de producción)

ETAPA 3.(1S)-2-morfolin-4-il-1-feniletilcarbamato tert butilo

La mezcla de 25 g (0.0792 mol)de metanosulfato de(2S)-2-[(terc-butoxicarbonil) amino]-2-feniletilo y morfolina (69.37 mL, 0.792 mol) en 250 mL de THF seco bajo atmósfera inerte se pusieron bajo reflujo durante 8 horas. La reacción fue entonces enfriada a temperatura ambiente, tratada con dietileter y el sólido fue filtrado. La solución fue evaporada proporcionando el crudo como un aceite amarillo que fue purificado a través de cromatografía de gel de sílice (eluente hexano/etilacetato 6/4). 11.59 g del producto titulado fueron aislados (48 %de producción).

ETAPA 4.dihidrocloruro (1S)-2-morfolin-4-il-1-feniletanamina

Una solución de 11.58 g (0.0378 mol) de (1S)-2-morfolin-4-il-1- feniletilcarbamato de terc butilo en 100 mL de diclorometano fueron tratados con 120 mL de HCl 4M en dioxano y agitados durante 18 horas. La mezcla fue diluida con dietileter y el producto filtrado (9.48 g, 90 % de producción).

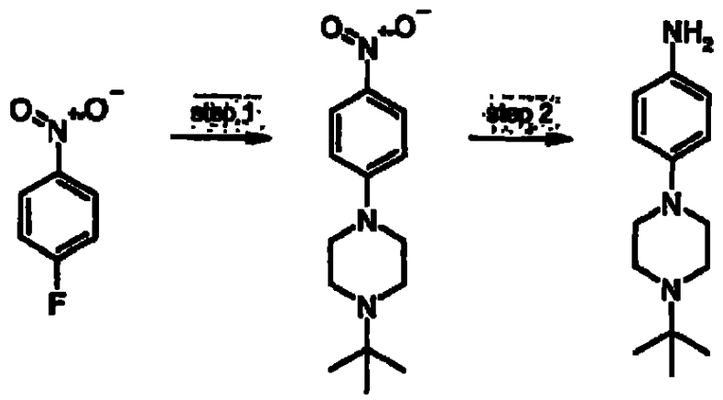
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.37 (m, 6 H) 3.83 (m, 4 H) 4.90 (m, 1 H) 7.51 (m, 5 H) 8.84 (bs, 3 H).

Trabajando de manera análoga los siguientes compuestos fueron preparados: trihidrocloruro de(1S)-2- (4-metilpiperazin-1-

000573
573

il)-1-feniletanamina ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (m, 13 H) 4.47 (m, 1 H) 7.46 (m, 5 H) 8.45 (bs, 3 H) 10.40 (bs, 1 H).

EJEMPLO 65



ETAPA.1 1-terc-butil-4-(4-nitrofenil) piperazina

Una solución de 800 mg (5.67 mmol) de 1-fluoro4-nitrobenzeno, 2.07 g (1.2 mmol) de dihidrobromuro 1- terc-butilpiperazina y 3.2 mL (20.41 mmol) de trietilamina, en 22 mL de acetriotilo, fueron puestos a reflujo durante 10 horas. La mezcla fue enfriada a temperatura ambiente, diluida con agua y extraída con diclorometano. La capa orgánica fue lavada con agua y solución salina, secada sobre Na_2SO_4 y evaporada. La purificación por cromatografía flash (eluente diclorometano/metanol 7/3) proporciono 860 mg del compuesto titulado como sólido amarillo.

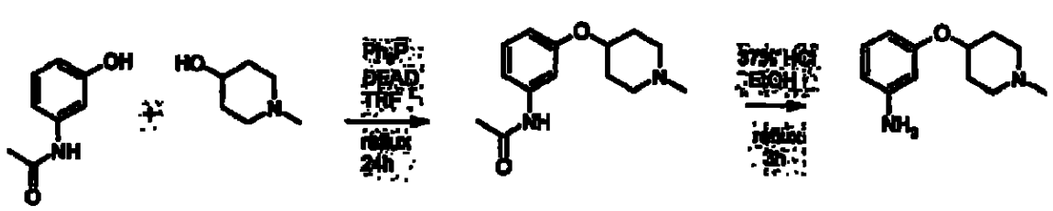
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 9 H) 2.63 (m, 4 H) 3.43 (m, 4 H) 7.03 (d, 2 H) 8.05 (d, 2 H).

ETAPA 2. 4-(4-terc-butilpiperazin-1-il) fenilamina

A una solución de 840 mg (3.189 mmol) de 1-terc-butil-4-(4-nitrofenil) piperazina en 24 mL de metanol, se disolvió 904 mg (16.9 mmol) de cloruro de amonio en 6 mL de agua y 552 mg (9.886 mmol) de hierro fueron agregados. Después de 7 horas, la suspensión fue enfriada y filtrada. El pH fue ajustado 10. por medio de agregar por porciones Na_2C0 a la fase acuosa. La extracción con diclorometano proporcionó 667 mg de la amina titulada.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.05 (s, 9 H) 2.62 (m, 4 H) 2.89 (m, 4 H) 4.52 (s, 2 H) 6.50 (d, J=8.78 Hz, 2 H) 6.67 (d, J=8.78 Hz, 2 H).

EJEMPLO 66



N-[3-(1-Metil-piperidin-4-iloxi)-fenil]-acetamida

Una suspensión de N-(3-Hydroxi-fenil)-acetamida (30.2 g) en tetrahidrofurano anhidro (600 mL) fue tratada con 4-hidroxi-N-metilpiperidina (30.54 mL) y trifenilfosfina (68.18 g); una solución de dietilazadicarboxilato en tetrahidrofurano anhidro (THF) (40.94 mL en 60 mL of THF) fue agregado gota a gota y la mezcla fue agitada a temperatura ambiente durante 2 horas y luego calentada 50°C durante la noche.

Cantidades adicionales de trifenilfosfina (28.00 g) y dietilazadicarboxilato (14 mL) se agregaron y el calentamiento se continuo durante 24 horas adicionales

El disolvente fue removido bajo vacío y el residuo fue retirado con acetato de etilo (600 mL), y extraído con acido clorhídrico 2N (3 x 200 mL). La capa acuosa fue lavada con acetato de etilo y el pH fue llevado a 10 por medio de agregar hidróxido de sodio al 20%. La extracción con acetato de etilo (4 x 100 mL) fue llevada a cabo y los extractos orgánicos combinados fueron lavados con solución salina y secados sobre sulfato de sodio anhidro. El disolvente fue removido bajo vacío y el crudo fue purificado por cromatografía flash sobre gel de sílice (eluente diclorometano/metanol 85: 15 luego + 0.1% trietilamina) para proporcionar 21 g del compuesto deseado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52-1.68 (m, 2 H) 1.83-1.96 (m, 2 H) 2.01 (s, 3 H) 2.14 (s, 3 H) 2.46-2.52 (m, 2 H) 2.

52-2.63 (m, 2 H) 4.18-4.20 (m, 1 H) 6.59 (d, 1 H) 7.05 (d, 1 H) 7.14 (t, 1 H) 7.26 (s, 1 H) 9.83 (s, 1H).

3-(1-Metil-piperidin-4-iloxi)-fenilamina

Una solución de N-[3-(1-Metil-piperidin-4-iloxi)-fenil]-acetamida (2.604 g) en etanol absoluto (40 mL) fue tratada con 37% de acido clorhídrico y la solución fue calentada a reflujo durante 3 horas.

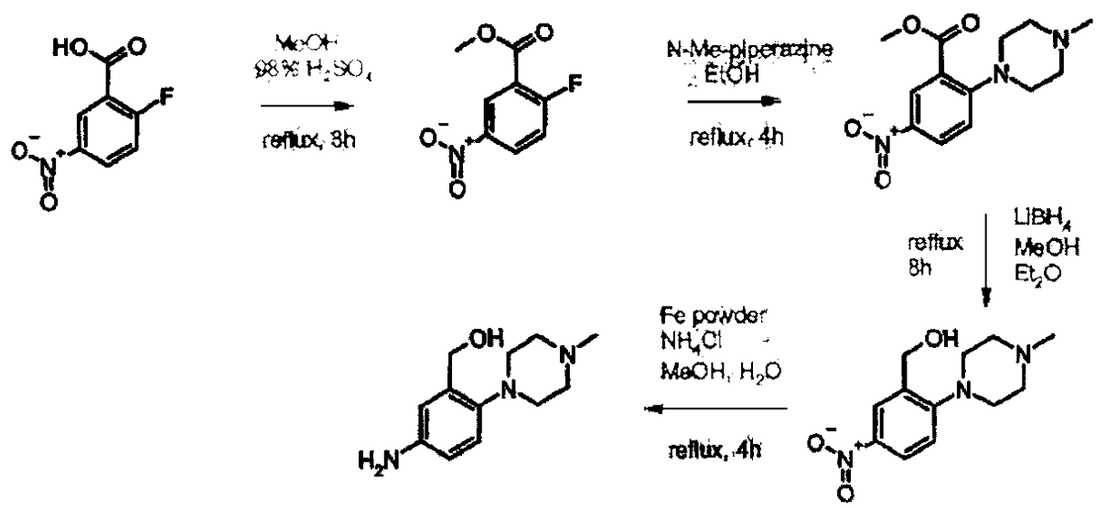
Después de remover el disolvente bajo vacío, el residuo fue disuelto en agua y lavado con acetato de etilo (30 mL). La solución acuosa fue basificada por hidróxido de sodio 20% y extraída con acetato de etilo (40 x 50 mL); las capas orgánicas combinadas fueron lavadas con solución salina (4 x 20 mL), con agua (2 x 10 mL) y secadas sobre sulfato de sodio anhidro. Después de remover el disolvente, el crudo (2.00 g) fue cristalizado a partir de n-hexano y acetato de etilo para proporcionar 1.00 g de compuesto puro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.54-1.68 (m, 2 H) 1.82-1.94 (m, 2 H) 2.12- 2.27 (m, 2 H) 2.21 (s, 3 H) 2.58-2.71 (m, 2 H) 4.14-4. 29 (m, 1 H) 4.98 (s, 2 H) 6.09 (ddd,.J=8.11,2.32,0. 79 Hz, 1 H) 6.14 (ddd, J=7.83,2.04,0.98 Hz, 1 H) 6.16 (t, J=2. 19 Hz, 1 H) 6.88 (t, J=7.99 Hz, 1 H)

EJEMPLO 67

00057
577

5-Amino-2-(4-metil-piperazin-1-il)-fenil]-metanol



2-fluoro-5-nitro-benzoato de metilo

Una solución de ácido 2-fluoro-5-nitro-benzoico (3.702 g,20mmol)en metanol anhidro (10,00 ml) fue tratada con 98% de acido sulfúrico y la solución fue calentada a reflujo durante 4 horas. El disolvente fue removido bajo vacío y el residuo fue disuelto en acetato de etilo (50ml). La solución fue lavada con bicarbonato de sodio acoso saturado (3 x 10 ml), solución salina hasta la neutralidad y luego agua,y secada sobre sulfato de sodio anhidro. El disolvente fue removido bajo vacío para proporcionar un aceite grueso que comenzó a cristalizar. Después de agregar n-hexano (3 ml) el crudo fue

almacenado durante 2 días en refrigerador. El compuesto cristalino fue filtrado y lavado con n-hexano para proporcionar 3.147 g del compuesto puro.

Por medio de concentrados los licores madre una segunda cosecha fue obtenida (390 mg)(y=89%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 7.69 (m, 1 H) 8.55 (m,1 H) 8.65 (m,1 H)

2-(4-metil-piperazin-1-il)-5-nitro-benzoato de metilo

Una solución de 2-fluoro-5-nitro-benzoato de metilo (3.487 g, 17.511 mmol) y N- metilpiperazina (3.855 mL, 3.508 g, 35.022 mmol) en 30 mL de metanol anhidro fueron calentados a reflujo durante 5 horas.

Después de remover los volátiles a presión reducida, el aceite naranja crudo fue tratado lentamente con agua (cerca de 20 mL) y agitado en un baño de hielo durante 1 hora. El compuesto cristalino formado fue filtrado por filtración con succión, lavado con agua y secado a 40°C bajo vacío durante 24 horas. Se obtuvieron 4.627 g de compuesto amarillo (producto 96%).

^{1}H NMR (400 MHz DMSO-d_6) δ ppm 2.25 (s 3 H) 2.46 (m 4 H) 3.27 (m 4 H) 3.87 (s, 3H) 7.22 (dj=9.27Hz, 1H) 8.08 (ddJ=9.27Hzj=2.80Hz, 1H) 8.33 (dJ02.80Hz, 1H)

2- (4-Metil-piperazin-1-il)-5-nitro-fenil]-metanol

Una suspensión de 2- (4-metil-piperazin-1-il)-5-nitro-bensoato de metilo (1.40 g, 5.00 mol) en dietil eter anhidro (60 ml) fue tratado con hidruro de litio boro (190.5 mg, 8.75 mol) y la formación de un precipitado fue observada. Se agrego entonces metanol Anhidro (0.350 ml, 280.3 mg, 8.75 mol) y la solución se calentó a reflujo durante 2 horas. Mientras la reacción no fue completa, se agrego hidruro de litio boro (190.5 mg) y metanol (0.350 ml) dos veces cada 4 horas.

Después de enfriar en un baño de hielo, la mezcla de reacción fue tratada con agua, con IN HCl (6 ml) y agitada a temperatura ambiente durante 15 minutos. La solución entonces fue bacificada a un pH 11 por hidróxido de sodio al 1N y extraída con diclorometano; los extracto orgánicos fueron lavados con solución salina y con agua y secado sobre sulfato de sodio Anhidro. El disolvente fue evaporado hasta el secado para proporcionar 1,35 g de un sólido carmelito que fue purificado por cromatografía flash sobre gel de sílice

(eluyente diclorometano/metanol 95: 5) para proporcionar 1,10 g del compuesto deseado (Producto 87%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s,3H) 2.52 (m,4H) 3.03 (m,4H) 4.54 (m,2H) 5.53 (t,1H) 7.17 (d J=8.90 Hz,1H) 8.08 (dd J=8.90 Hz J=2.92 Hz,1H) 8.33 (d J=2.92 Hz,1H).

5-Amino-2- (4-metil-piperazin-1-il)-fenil]-metanol

a una solución de [2- (4-Metil-piperazin-1-il)-5-nitro-fenil]-metanol crudo (437 mg, 1.74 mol) en metanol (1.5 ml), se agrego cloruro de amoniaco (NH_4Cl) (465 mg), agua (4.9 mL) y polvo de Fe (290 mg) y la mezcla se calentó a 100°C durante 3 horas.

La mezcla de reacción fue filtrada y el precipitado negro lavado con MeOH/agua 1: 1 (10 mL). El Metanol fue removido bajo vació y el agua restante fue bacificada con carbonato de sodio (Na_2CO_3) y extraída con acetato de etilo (5 x 20 mL).

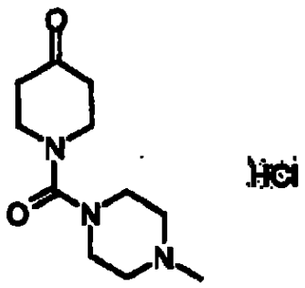
Los extractos orgánicos fueron lavados con solución salina (2 x 10 mL) y con agua (2 x 5 mL) y secado sobre sulfato de sodio anhidro. Después de la evaporación, el sólido naranja crudo resultante fue purificado por cromatografía flash sobre gel de sílice (eluyente diclorometano/metano/trietilamina 90:

10: 0.1) para proporcionar 357 mg del compuesto titulado puro (producto 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.26 (s,3H) 2.52 (m,4H) 2.73 (m,4H) 4.48 (m,2H) 4.75 (bs,2H) 4.95 (t,1H) 6.43 (dd J=8.42 Hz J=2.68 Hz,1H) 6.67 (d J=2.68 Hz,1H) 6.80 (d J=8.42 Hz,1H).

Ejemplo 68

Clorhidrato 1-(4-metil-piperazina-1-carbonil-piperidin-4-ona



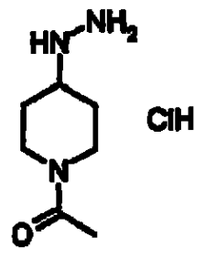
A una suspensión clorhidrato de cloruro de 4- metil piperazina -1-carbonilo (19.9g 0.1 mol) y clorhidrato de monohidrato de piperidona (15.3g 0.1 mol), en 200 mL de diclorometano, se agregó gota agota trietilamina (45 mL, 0.33 mol). La mezcla fue agitada durante 2 horas. La fase orgánica fue lavada con solución salina (2 x 20 mL) y secada sobre sulfato de sodio. Después de filtrado, el disolvente fue evaporado en vacio y el producto crudo fue disuelto en EtOH (50 mL) y dietileter (100 mL) y se trato con HCl 4N en dioxano (25 mL). Después de una hora el precipitado fue

filtrado y secado en horno para dar 13 g (producto 50%) del compuesto titulado.

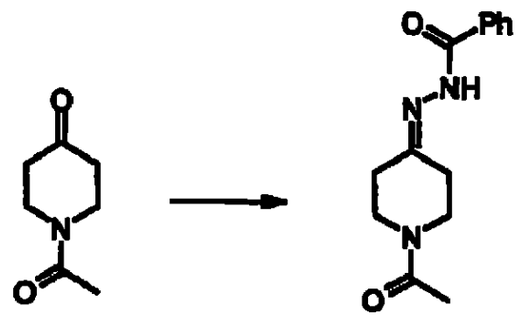
1H NMR (400 MHz, DMSO-D6) δ ppm 2.40 (t, J=6.16 Hz,4H) 2.81 (s,3H) 3.00- 3.11 (m,2H) 3.12-3.23 (m,2H) 3.28-3.42 (m,2H) 3.51 (t, J=6.16 Hz,4H) 3.73 (d, J=14.27 Hz,2H) 10.12 (s,1H)

Ejemplo 69

Clorhidrato 1-acetil-4-hidrazinopiperidina



Etapa 1: N'-(1-acetilpiperidin-4-ilidene)benzohidrazida

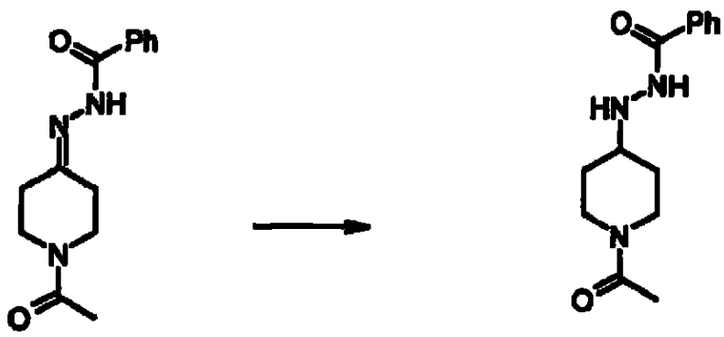


20g (0.142 mol) de 1-acetil-4-piperidona fueron disueltos en 400 mL de etanol absoluto y 21.2g (0.156 mol) de benzoilhidrazina que fueron agregados. La solución resultante

fue puesta en reflujo durante 6 horas bajo agitación. El disolvente fue entonces removido en vació y el residuo fue particionado entre diclorometano y agua. La capa orgánica fue secada sobre sulfato de sodio y evaporada hasta secado. Y el residuo fue triturado con dietileter y 30g (83 % del producto) del compuesto titulado fue recolectado por filtración.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.07 (s,3H) 2.43-2.62 (m,4H) 3.45-3.74 (m,4H) 7.51 (m,3H) 7.84 (m,2H) 10.7 (bs,1H).

Etapa 2: N'- (1-acetilpiperidin-4-il) benzohidrazida

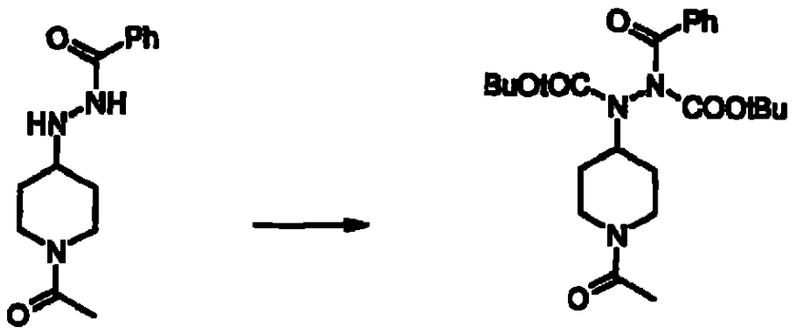


30g (0.12 mol) de N'- (1-acetilpiperidin-4-ilidene) benzohidrazida fueron disueltas en 500 mL de ácido acético glacial y 1 g de PtO_2 fueron agregados. La mezcla fue hidrogenada a 40 psi durante 12 horas a temperatura ambiente. El catalizador fue entonces filtrado sobre celita y el

filtrado evaporado en vació. El residuo fue redisuelto con diclorometano y lavado con $NaHCO_3$. El disolvente fue secado sobre sulfato de sodio y removido bajo presión reducida para dar, después de trituración con dietileter, 28.6g (92 % del producto) del compuesto titulado.

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (m,2H) 1.81 (m,2H) 2.00 (s,3H) 3.75 (m,2H) 4.10 (m,2H) 4.19 (s,1H) 7.49-7.51 (m,3H 7.84 (m,2H) 10.01 (s,1H).

Etapa 3: **1- (1-acetilpiperidin-4-il)-2-benzoilhidrazina-1, 2-dicarboxilato di-terc-butilo**

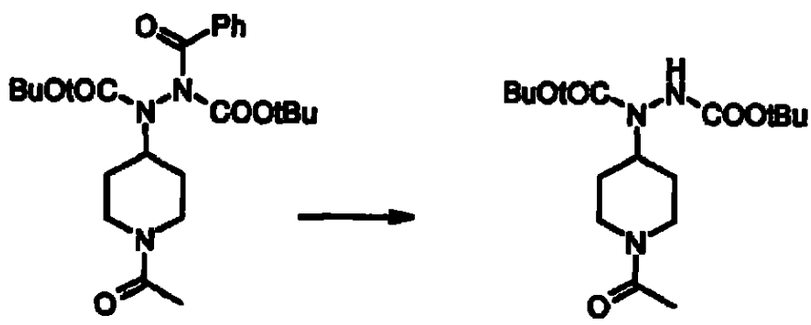


A una solución de 28.6g (0.11 mol) de N'-(1-acetilpiperidin-4-il) benzohidrazida en 700 mL de acetonitrilo, se agregaron 53.19g (0.44 mol) de 4-dimetilaminopiridina (DMAP) y 77.2g (0.35 mol) de di-terc-butildicarbonato. La mezcla fue agitada durante la noche, el disolvente removido y el residuo retirado con diclorometano y lavado con KHSO4 acuoso para

remover DMAP. La capa orgánica fue secada sobre sulfato de sodio y evaporizada para dar 45g del compuesto titulado como un aceite.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 y 1.40 (2s, 18H) 1.97 (s,3H) 4.28 (m,1H) 7.51-7.53 (m,4H).

Etapa 4: **1- (1-acetilptpendin-4-il) hidrazina-1, 2-dicarboxilato di-terc-butilo**

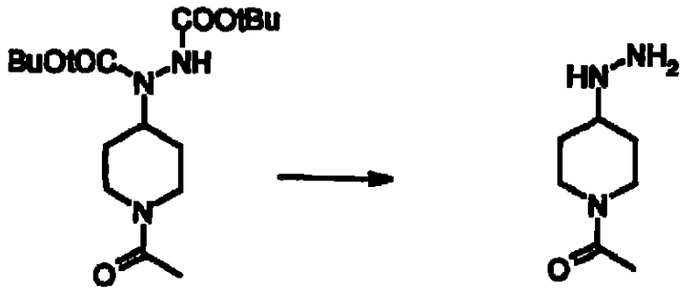


45g (0.1 mol) de 1-(1-acetilpiperidin-4-il)-2-benzoilhidrazina-1, 2- dicarboxilato de di-terc-butil fueron disueltos en 1 L de tetrahidrofurano y se agrego una solución de 5.8g (0.14 mol) de monohidrato de hidróxido de litio en 1 L la mezcla de agua fue agitada a temperatura ambiente durante 16 horas, el tetrahidrofurano fue removido en vació y la capa acuoso extraída varias veces con diclorometano. La

fase orgánica fue secada sobre sulfato de sodio y evaporada hasta secado, dando 32 g (84 % de producto) del compuesto titulado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 y 1.42 (2s,18H) 1.99 (s,3H) 4.09 (m,1H) 2.52 y 3.05/2m,4H) 3.95 y 4.41 (2m,4H) 8.81 (bs,1H).

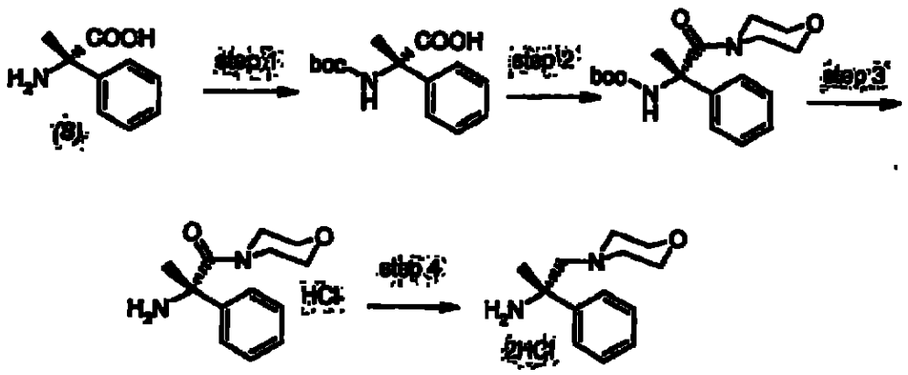
Etapa 5: clorhidrato 1-acetil-4-hidrazinopiperidina



32g (0.09 mol) de 1- (1-acetilpiperidin-4-il) hidrazina-1,2-dicarboxilato de di-terc-butil fueron disueltos en 300 mL de metanol y 30 mL de HCl 4 M en dioxano fueron agregados. La mezcla fue agitada a temperatura ambiente durante la noche. El disolvente fue entonces evaporado y el residuo cristalizado a partir de etanol, dando 14g (77% de producción) del compuesto titulado.

Ejemplo 70

diclorhidrato de (1S)-1-metil-2-morpholin-4-il-1-feniletilamina



Etapa 1:. N- (terc-butoxicarbonil)-2-fenil -D-alanina

A una suspensión de 500 mg de 2-fenil-D-alanina (3. 02 mmol) hidróxido de trimetilamonio (solución acuosa 10%, 2.8 mL, 3.02 mmol) en 15 mL de acetonitrilo, se agrego diterbutilcarbonato (1.047g, 4.8 mmol) y la mezcla fue agitada a temperatura ambiente durante 2 días. El disolvente fue entonces removido bajo vació, el residuo fue disuelto en agua y lavado con dietileter. La capa acuosa fue acidificada a un pH = 3-4 ácido cítrico y el producto fue extraído con acetato de etilo (3 x 20 mL). La fase orgánica combinada fue lavada con agua, secada sobre Na2S04 y evaporada. El producto titulado fue recuperado como un sólido blanco (630 mg, producción 78 %).

Etapa 2: N- (terc-butoxicarbonil)- (1S)-1-metil-2-morpholin-4-il-2-oxo-1- feniletilamina

630 mg (2.374 mmol) de N- (terc-butoxicarbonil)-2-fenil-D-alanina fueron disultas en 20 mL de DMF seco y se agrego tetrafluoborato de O-(benzotriazol-1-il)-1,1,3,3-tetrametiluronio (TBTU, 1.37g, 4.27 mmol), morpholina (0.412 mL, 4.73 mmol) y diisopropiletilamina (1.63 mL, 9.5 mol).La mezcla fue agitada a temperatura ambiente durante 1 hora, y luego el disolvente fue removido y el residuo disuelto con diclorometano. La solución fue lavada con $NaHCO_3$ saturada, solución salina, agua y secada sobre Na_2SO_4. 700 mg del compuesto titulado fueron recuperados (producción 88%).

^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.40 (s,9H) 1.65 (s,3H) 3.33 (m,8H) 7.35 (m,6H).

Etapa 3: clorhidrato (1S)-1-metil-2-morfolin-4-il-2-oxo-1-feniletilamina.

Una solución de 630 mg (1.884 mmol) de N- (terc-butoxicarbonil)- (1S)-1-metil-2- morpholin-4-il-2-oxo-1-feniletilamina en 20 mL de dioxano fueron tratados con 2.5 mL de HCl 4N en dioxano durante la noche. El disolvente fue removido bajo vació y el sólido fue triturado con dietileter produciendo 560 mg del compuesto titulado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (s,3H) 3.35 (m,8H) 7.51 (m,5H) 8.52 (bs,3H).

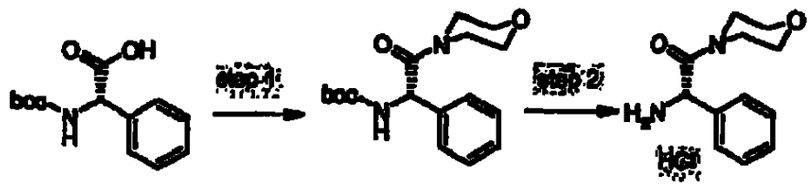
Etapa 4: diclorhidrato (1S)-1-metil-2-morfolin-4-il-1-feniletilamina.

Bajo una atmósfera de argón 412 mg de (clorhidrato) (1S)-1-metil-2-morflin-4-il-2-oxo-1- feniletilamina (1.522 mol) fueron disueltos en 30 mL de THF seco. Una solución al 2 M de dimetilsulfuro borano (4.4 mL, 5.78 mmol) fue agregado gota a gota a 0°C y la mezcla fue agitada durante 10 minutos a 0°C y luego se le permitió alcanzar la temperatura ambiente (evolución de gas). Depuse de 4 horas la reacción fue calmada con metanol (agregado muy cuidadosamente) y diluido con metanol cuando la efervescencia seso. El THF fue removido bajo vació y la solución metanólica fue calentada a 60°C durante 30 minutos. El disolvente fue por ultimo removido completamente recuperando 330 mg de la amina que fue disuelta subsecuentemente en 15 mL de dioxano y tratada con 1.35 mL de HCl 4 N en dioxano. Después de 1 hora el disolvente fue evaporado y el producto fue triturado con dietileter para proporcionar 350 mg de la sal esperada.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.66 (s,3H) 2.52 (m,6H) 3.57 (m,4H) 7.51 (m,5H) 8.53 (s,3H).

Ejemplo 71

Clorhidrato de (1S)-2-morfolin-4-il-2-oxo-1-feniletilamina



Etapa 1: N- (terc-butoxicarbonil)- (1S)-2-morpholin-4-il-2-oxo-1-feniletilamina

1g (3.98 mmol) de Boc-L-fenilglicina fueron disueltos en 18 mL de DMF seco y se agrego tetrafluoborato O- (benzotriazol-1-il)-1, 1, 3, 3-tetrametiluronio (TBTU, 1.92g, 5.97 mmol), morfolina (0.555 mL, 6.37 mmol) y diisopropiletilamina (2.72 mL, 15.92 mol). La mezcla fue agitada a temperatura ambiente durante 1 hora, luego el disolvente fue removido y el residuo disuelto con diclorometano. La solución fue lavada con $NaHCO_3$, saturada, solución salina, agua, y secada sobre Na_2SO_4. 1.327g del compuesto titulado fueron recuperados.

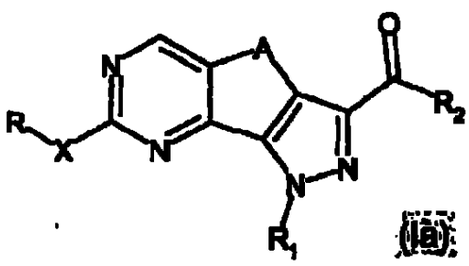
Etapa 2: clorhidrato (1S)-2-morfolin-4-il-2-oxo-1-feniletilamina

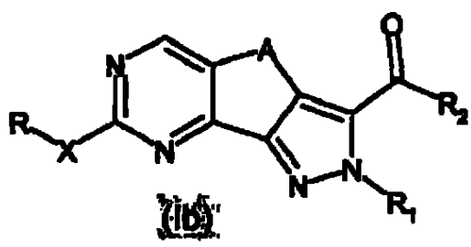
1.327 g de N-(terc-butoxiearbonil)-(1S)-2-morfolin-4-il-2-oxo-1-feniletilamina fueron disueltos en 15 mL de dioxano y tratados con 3.5 mL de HCI 4 M en dioxano durante la noche. El disolvente fue removido y el sólido fue triturado con dietileter proporcionando 920 mg del producto (producción 90%).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.13 (m,4H) 3.54 (m,4H) 5.58 (m,1H) 7.50 (s,5H) 8.58 (s,3H).

REIVINDICACIONES

1) Un derivado de pirazolo-quinazolina representado por la fórmula (Ia) o (Ib)


(Ia)


(Ib)

En donde R es hidrógeno o un grupo opcionalmente sustituido seleccionado de amino, alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_{10}, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo;

X es un enlace sencillo o un radical divalente seleccionado de -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- o -SO_2-, en donde R' es hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R y R' pueden formar un grupo heteroarilo o heterociclilo de 5 a 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

R_1, unido a uno cualquiera de los átomos de nitrógeno del anillo de pirazolo como por las fórmulas (Ia) o (Ib), representa un átomo de hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, en la fórmula (Ib), R_1 es un grupo divalente $-(CH_2)_n-NH-$ que está ligado a R_2 en donde n es 2 o 3;

R_2 es un grupo seleccionado de -NR''R''',-N(OH)R'',-OR'' o -R'', en donde R'' y R''' son, cada uno independientemente, hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R'' y R''' pueden formar un grupo heteroarilo o heterociclilo de 5 o 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

A es un grupo divalente seleccionado de $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ o -CH=CH-; o una sal farmacéuticamente aceptable de estos.

2) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -NH- y R_2 es un grupo seleccionado de -NHR'',-N(OH)R'',-OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado entre cicloalquilo C_3-C_6 o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

3) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -O- y R_2 es un grupo seleccionado entre -NHR'',-N(OH)R'',-OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado entre cicloalquilo C_3-C_6 o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

4) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -S- y R_2 es un grupo seleccionado entre -NHR'',-N(OH)R'',-OR'' o -R'', en donde R'' es un grupo opcionalmente sustituido seleccionado entre cicloalquilo C_3-C_6 o cicloalquil-alquilo, arilo, arilalquilo,

heterociclilo o heterociclilalquilo; y R, R_1 y A son como se definió anteriormente.

5) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -NH- y R_2 es un grupo -NHR'' o -N(OH)R'' en donde R'' es un átomo de hidrógeno o un grupo alquilo C_1-C_4 recto o ramificado; y en donde A, R y R_1 son como se definió anteriormente.

6) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -O- y R_2 es un grupo -NHR'' o -N(OH)R'' en donde R'' es un átomo de hidrógeno o un grupo alquilo C_1-C_4 recto o ramificado; y en donde A, R y R_1 son como se definió anteriormente.

7) Un compuesto de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, en donde X es un grupo -S- y R_2 es un grupo -NHR'' o -N(OH)R'' en donde R'' es un átomo de hidrógeno o un grupo alquilo C_1-C_4 recto o ramificado; y en donde A, R y R_1 son como se definió anteriormente.

8) Un compuesto de fórmula (Ib), de acuerdo con la reivindicación 1, en donde R, X y A son como se definió anteriormente y R_1 y R_2 están ligados juntos por medio de un $-(CH_2)_n-NH-$ divalente en donde n es como se definió anteriormente.

9) Un compuesto de fórmula (Ia) o (Ib) de acuerdo con la reivindicación 1, en donde A es un grupo seleccionado entre $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$ o $-C(CH_3)_2-CH_2-$.

10) Un compuesto de fórmula (Ia) o (Ib) de acuerdo con la reivindicación 1, en donde cualquiera de los anteriores R, R', R_1, R'' y R''' pueden ser sustituidos opcionalmente en cualquiera de sus posiciones libres por uno o más grupos independientemente seleccionados entre: halógeno, nitro, grupos oxo (=O), ciano, azido, alquilo, alquilo polifluorinado, hidroxialquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, cicloalquilo, alquilarilo, alquilheterociclilo, hidroxi, alcoxi, alcoxi polifluorinado, ariloxi, arilalquiloxi, heterocicliloxi, heterociclilalquiloxi, metilenodioxi, alquilcarboniloxi, alquilcarboniloxialquilo, arilcarboniloxi, carboxi, alcoxicarbonilo,

alcoxicarbonilalquilo, ariloxicarbonilo, cicloalquiloxicarbonilo, amino, aminoalquilo, alquilaminoalquilo, alquilaminoalquiloxi, ureido, alquilamino, dialquilamino, arilamino, diarilamino, formilamino, alquilcarbonilamino, arilcarbonilamino, heterociclilcarbonilamino, alcoxicarbonilamino, alcoxiimino, alquilsulfonilamino, arilsulfonilamino, formilo, alquilcarbonilo, arilcarbonilo, heterociclilcarbonilo, cicloalquilcarbonilo, heterociclilcarbonilo, aminocarbonilo, alquilaminocarbonilo, dialquilaminocarbonilo, arilaminocarbonilo, alquilsulfonilo, arilsulfonilo, heterociclilsulfonilo, aminosulfonilo, alquilaminosulfonilo, dialquilaminosulfonilo, ariltio y alquiltio.

11) Cualquier compuesto específico de fórmula (Ia) o (Ib), de acuerdo con la reivindicación 1, opcionalmente en la forma de una sal farmacéuticamente aceptable, entre aquellas definidas en las tablas VI a XXI.

12) Un método para tratar desórdenes proliferativos celulares causados por y/o asociados con una actividad de la proteína quinasa alterada, por medio

de administrar a un mamífero que lo necesite una cantidad efectiva de un derivado de pirazolo-quinazolina representado por la fórmula (Ia) o (Ib) . como se establece en la reivindicación 1.

13) El método de acuerdo con la reivindicación 12, en donde la actividad de la proteína quinasa es la actividad Aurora 2.

14) El método de acuerdo con la reivindicación 12, en donde la actividad de la proteína quinasa es el ciclo celular dependiente de actividad de quinasa.

15) El método de acuerdo con la reivindicación 12, en donde el desorden proliferativo celular es seleccionado entre el grupo que consiste de cáncer, enfermedad de Alzheimer, infecciones virales, enfermedades autoinmunes y desórdenes neurodegenerativos.

16) El método de acuerdo con la reivindicación 15 en donde el cáncer es seleccionado del grupo que consiste de carcinoma, carcinoma de célula escamoso; tumores hematopoyéticos de linaje linfoide, tumores de origen mesenquimal, tumores del sistema nervioso

central y periférico, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentoso, queratoxantoma, cáncer folicular de la tiroides y sarcoma Kaposi.

17) El método de acuerdo con la reivindicación 12, en donde el desorden proliferativo celular es seleccionado del grupo que consiste de hiperplasia benigna de próstata, poliposis de adenomatosis familiar, neurofibromatosis, soriasis, proliferación celular suave vascular asociada con ateroesclerosis, fibrosis pulmonar, artritis, glomerulonefritis y estenosis y restenosis post-quirúrgica.

18) El método de acuerdo con la reivindicación 12 que suministra angiogénesis de tumor e inhibición de metástasis lo mismo que tratamiento de rechazo de transplante de órganos y enfermedad de injerto versus huésped.

19) El método de acuerdo con la reivindicación 12 que suministra tratamiento o prevención de alopecia inducida por radioterapia o inducida por qiomioterapia.

20) El método de acuerdo con la reivindicación 12 que comprende adicionalmente someter el mamífero en necesidad de esto a una terapia de radiación o a un régimen de quimioterapia en combinación con por lo menos un agente citostático o citoetoxi.

21) El método de acuerdo con la reivindicación 12 en donde el mamífero que lo necesita es un humano.

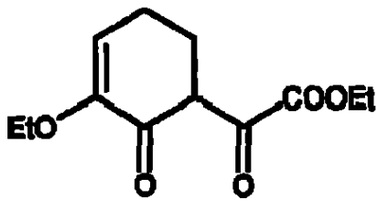
22) Un método para inhibir la actividad Aurora 2 quinasa que comprende poner en contacto dicha quinasa con una cantidad efectiva de un compuesto según se definió en la reivindicación 1.

23) Un método para inhibir la actividad de quinasa dependiente de ciclina que comprende poner en contacto dichas quinasas con una cantidad efectiva de un compuesto según se definió en la reivindicación 1.

24) Un proceso para preparar los compuestos de fórmula (I), que comprende los compuestos de fórmula (Ia) o (Ib) según se definió en la reivindicación 1, o las sales farmacéuticamente aceptables de los mismos, dicho proceso comprende:

(1) cuando A es un grupo - $(CH_2)_2$-:

et.1) hace reaccionar 2-etoxi-2-ciclohexen-1-ona con dietiloxolato, en la presencia de litio (bis-trimetilsilil) amida [$LiN(TMS)_2$], con el fin de obtener un compuesto de la fórmula (II)

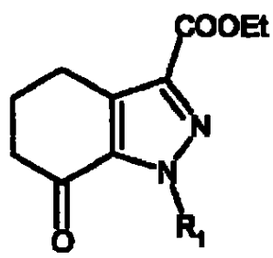


(II)

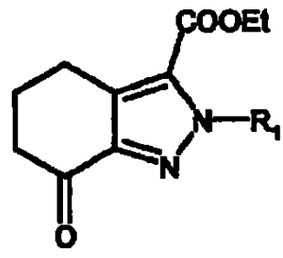
y tratarlo con un derivado de hidracina de la fórmula (III)

$$R_1\text{-}NHNH_2 \quad (III)$$

En donde R_1 es como se definió anteriormente, de acuerdo a las condiciones operativas establecidas en cualquiera de las etapas (et. 2a), (et. 2b) o (et. 2c) et. 2a) en la presencia de un alcohol inferior con el fin de obtener un mezcla de los compuestos de fórmula (IVa) y (IVb)



(IVa)



(IVb);

En donde R_1 es como se definió anteriormente, y separar su mezcla en los compuestos simples, (IVa) y (IVb);

et. 2b) en la presencia de acido acético con el fin de obtener un compuesto de fórmula (IVa);

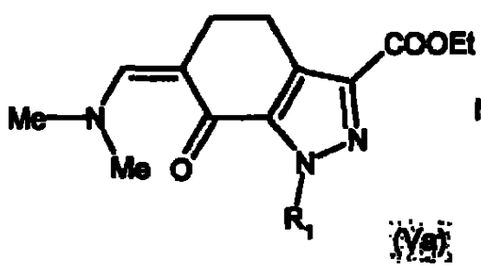
et. 2c) al aquilatar un compuesto de fórmula (IVa) que es obtenido en la etapa (et. 2a) o (et. 2b) y en donde R_1 es hidrógeno con los compuestos de fórmula (IVc)

$$R_1Y \quad (IVc)$$

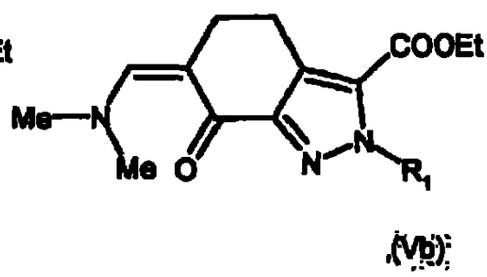
En donde Y es un grupo saliente adecuado como mesilo, tosilo, halógeno con el fin de obtener una mezcla de compuestos fórmula (IVa) y (IVb) en donde R_1 es como se definió anteriormente y separar su mezcla en los compuestos (IVa) y (IVb);

et.3) hacer reaccionar el compuesto de fórmula (IVa) preparado de acuerdo con una cualquiera de las etapas (et.2a), (et.2b) o (et.2c), o de fórmula (IVb) preparado

de acuerdo con las etapas (et.2a) o (et.2c), con dimetilformamida-di-terc-butilacetal para obtener un compuesto de fórmula (Va) o (Vb).

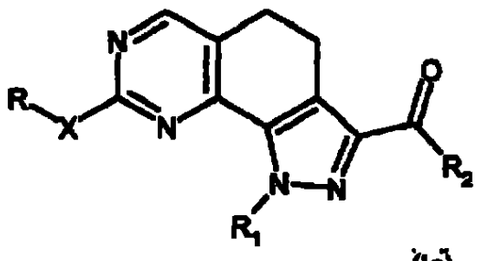


(Va)

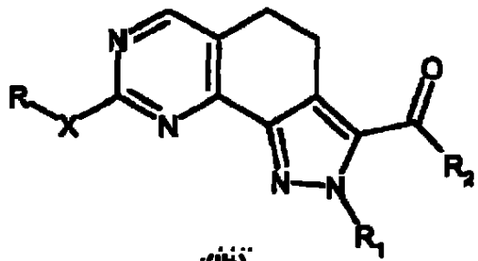


(Vb)

En donde R_1 es como se definió anteriormente; y hacer reaccionar el compuesto de fórmula (Va) o (Vb) de acuerdo una cualquiera de las etapas alternativas (et. 4a), (et. 4b) o (et. 4c) et. 4a) con guanidina con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



(Ia)



(Ib)

Donde R-X-es amino, R_2 es etoxi, y R_1 es como se definió anteriormente; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4b) con un derivado de guanidina de fórmula (VI)

$$R\text{-}NH\text{-}C(=NH)NH_2 \quad (VI)$$

donde R es como se definió anteriormente con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R y R_1 son como se definió anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4c) con una alquilisotiourea de fórmula (VII)

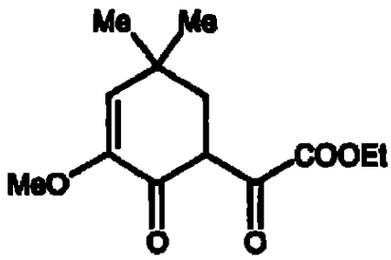
$$R\text{-}S\text{-}C(=NH)NH_2 \quad (VII)$$

Donde R es como se definió anteriormente con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R y R_1 son como se definió anteriormente, X -S- y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

et. 4d) con metilisourea con el fin de obtener un compuesto de fórmula (Ia) o (Ib) donde R_1 es como se definió anteriormente R es metilo, X es -O- y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

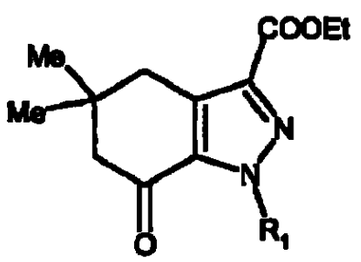
(2) cuando A es un grupo $-C(CH_3)_2-CH_2-$:

et. 5) hacer reaccionar 2-metoxi-4,4-dimetil-2-ciclohexen-1-ona con dietil oxalato, en la presencia de $[LiN(TMS)_2]$,con el fin de obtener un compuesto de fórmula (VIII)

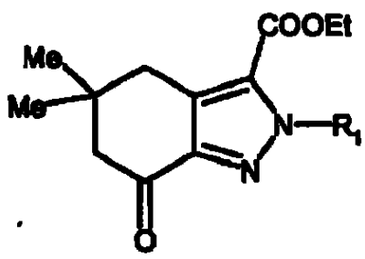


(VIII)

et. 6) hacer reaccionar el compuesto de fórmula (VIII) con un derivado de hidracina de fórmula (III) de acuerdo a una cualquiera de las etapas previas (et. 2a) o (et. 2b) con el fin de obtener un compuesto de fórmula (IXa) o (IXb)



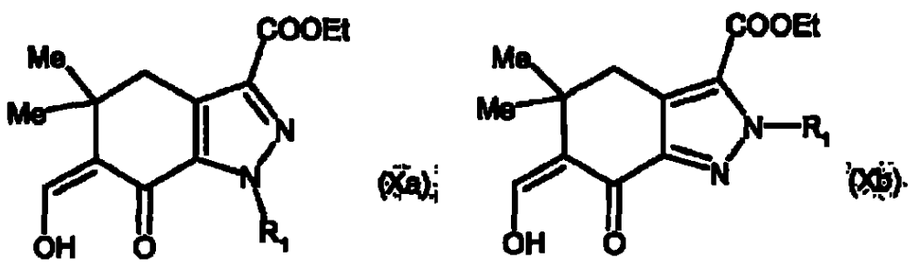
(IXa);



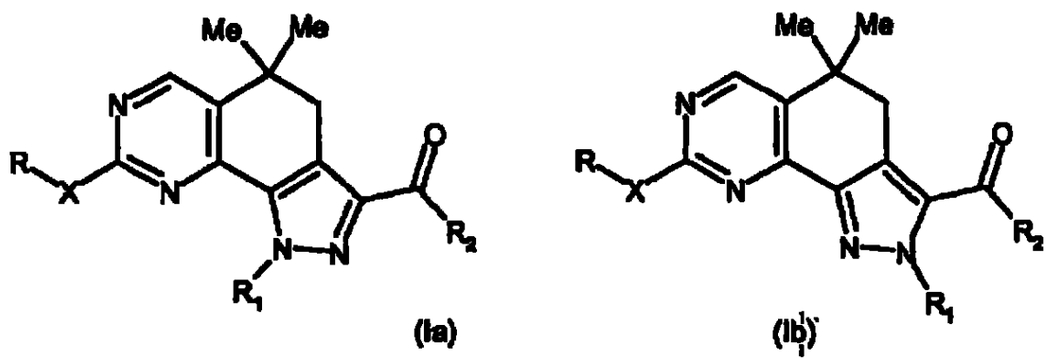
(IXb);

en donde R_1 es como se definió anteriormente;

et. 7) hacer reaccionar el compuesto de fórmula (IXa) o (IXb) con formato de etilo en condiciones básicas con el fin de obtener un compuesto de fórmula (Xa) o (Xb)



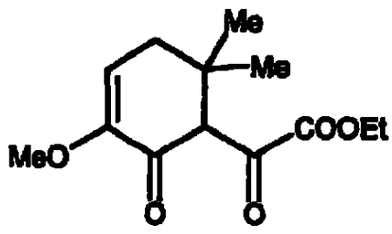
et. 8) hacer reaccionar el compuesto de fórmula (Xa) o (Xb) con guanidina o un derivado de guanidina de fórmula (VI), con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



en donde R y R_1 son como se definió anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

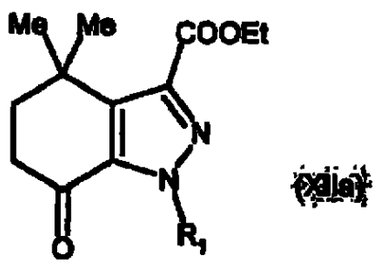
(3) cuando A es un grupo $-CH_2-C(CH_3)_2-$:

et. 9) hacer reaccionar 2-metoxi-5,5-dimetil-2-ciclohexen-1-ona con dietil oxalato en la presencia de hidruro de sodio, con el fin de obtener un compuesto de fórmula (XI)

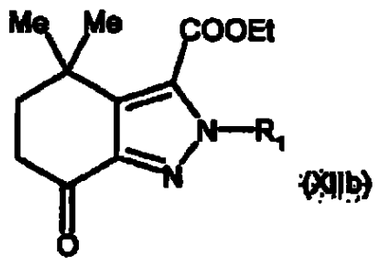


(XI)

et. 10) hacer reaccionar un compuesto de fórmula (XI) con derivado de hidracina de fórmula (III) de acuerdo a una cualquiera de las etapas (et. 2a) o (et. 2b) con el fin de obtener un compuesto de fórmula (XI o (XIIb)



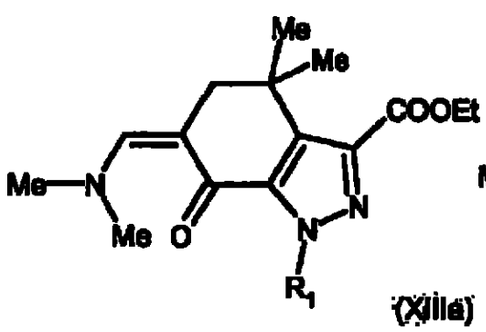
(XIIa)



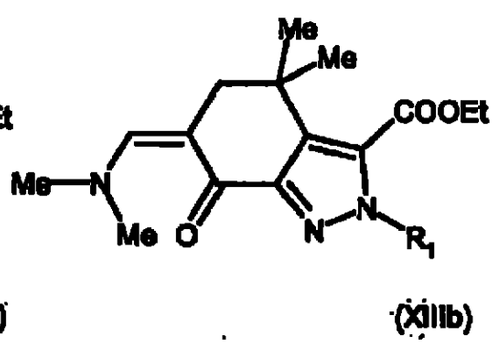
(XIIb)

en donde R_1 es como se definió anteriormente;

et. 11) hacer reaccionar el compuesto de fórmula (XIIa) o (XIIb) con dimetilformamida-di-terc-butilacetalo con el fin de obtener un compuesto de fórmula (XIIIa) o (XIIIb)

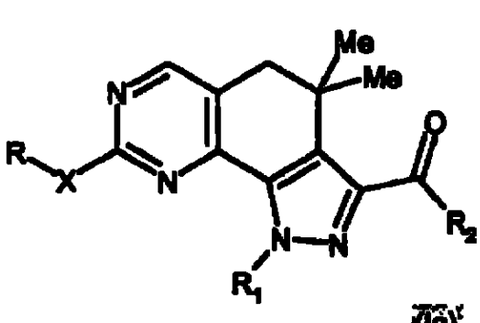


(XIIIa)

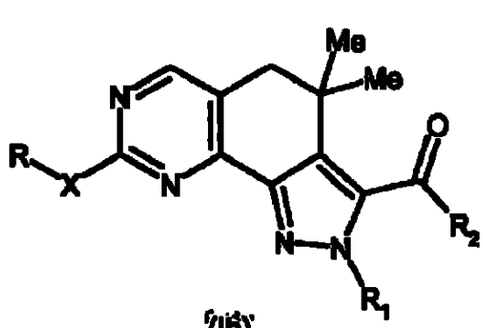


(XIIIb)

et. 12) hacer reaccionar un compuesto de fórmula (XIIIa) o (XIIb) con un derivado de guanidina de fórmula (VI), con el fin de obtener un compuesto de fórmula (Ia) o (Ib)



(Ia)

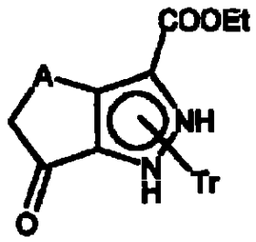


(Ib)

En donde R y R_1 son como se definió anteriormente, X es -NH-, y R_2 es etoxi; y opcionalmente convertirlos en otros derivados de fórmula (I);

(4) cuando, en la fórmula (Ib), R_1 está directamente ligado a R_2 con el fin de producir una estructura de anillo tetracíclica:

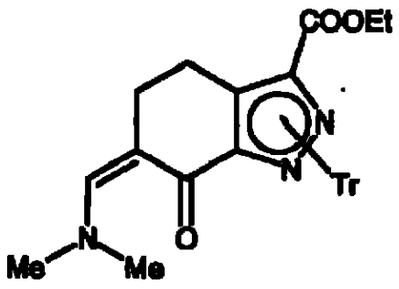
et.13) Hacer reaccionar un compuesto de fórmula (IV) en donde R_1 es hidrógeno, obtenido de acuerdo a (et.2), del proceso, con cloruro de trifenilmetilo con el fin de obtener un compuesto de fórmula (XIV).



(XIV)

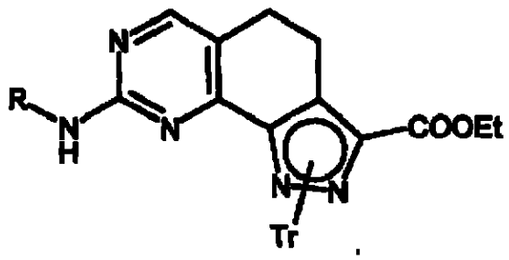
En donde Tr representa tritil(trifenimetil);

Et.14) hacer reaccionar el compuesto de fórmula (XIV) con dimetilformamida-di-terc-butilacetato, como se estableció en la etapa (et.3), con el fin de obtener un compuesto de fórmula (XV)



(XV)

et.15) hacer reaccionar el compuesto de fórmula (XV) con un derivado de guanidina adecuado de fórmula (VI), como se estableció en la etapa (et.4b), con el fin de obtener un compuesto de fórmula (Ia) o (Ib).



(Ia) or (Ib)

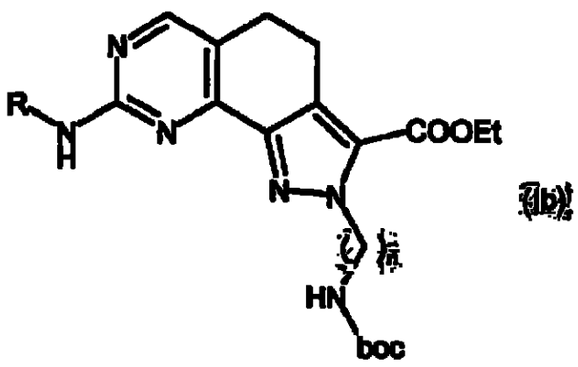
donde R es como se definio anteriormente, X es NH, R_1 es tritilo y R_2 es etoxi;

et.16) hacer reaccionar el compuesto anterior de la fórmula (Ia) o (Ib) bajo condiciones acídicas, con el fin de obtener el compuesto correspondiente de fórmula (Ia) o (Ib) en donde R_1 es hidrógeno;

et.17) hacer reaccionar el compuesto anterior de fórmula (Ia) o (Ib) con un agente aquilatante adecuado de fórmula (XVI) en la presencia terc-butilato de litio

$$Br-(CH_2)_n-NH-BOC \qquad (XVI)$$

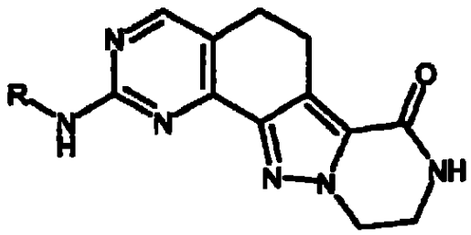
En donde n es 2 o 3, con el fin de obtener un compuesto de fórmula (Ib)



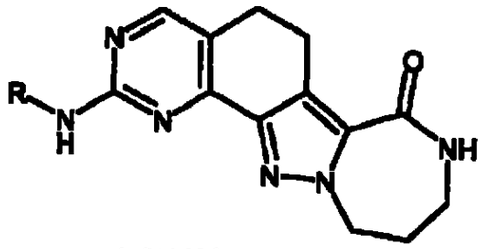
(Ib)

En donde n y R son como se definió anteriormente;

et.18) hacer reaccionar el compuesto anterior de fórmula (Ib) bajo condiciones ácidas, con el fin de convertir el grupo terc-butoxicarbonilamino en amino (desprotección) y hacerlo reaccionar con carbonato de cesio ($CsCO_3$) con el fin de obtener cualquiera uno de los dos compuestos de fórmula (Ib)



(Id; n=2)

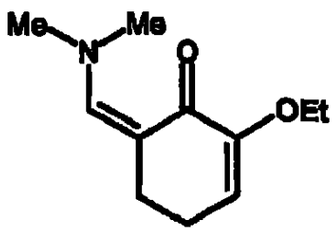


(Id; n=3)

En donde R es como se definió anteriormente, y opcionalmente convertirlos en otros derivados de fórmula (I);

(5) cuando R_2 es un grupo voluminoso:

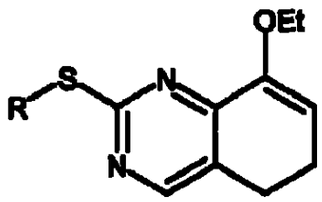
et.19) hacer reaccionar 2-etoxi-2-ciclohexenona con dimetilformamida-di-terc-butilacetalo, como se definió en la etapa (et.3), con el fin de obtener un compuesto de fórmula (XVII)



(XVII)

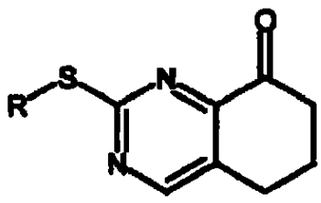
et.20) hacer reaccionar el compuesto de fórmula (XVII) con un derivado de fórmula (VII) de acuerdo a la etapa

(et.4c), con el fin de obtener un compuesto de la fórmula (XVIII)



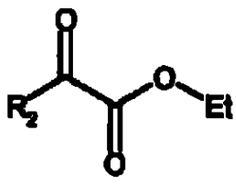
(XVIII)

En donde R es como se definió anteriormente; y subsecuentemente tratar este bajo de condiciones ácidas con el fin de obtener un compuesto de fórmula (XIX)



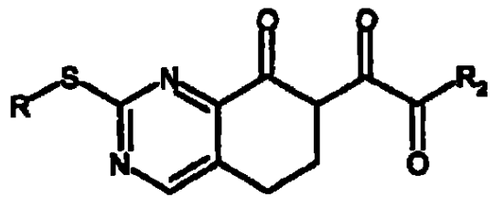
(XIX)

et.21) hacer reaccionar el compuesto de fórmula (XIX) con un compuesto de fórmula (XX)



(XX)

En donde R_2 es un grupo voluminoso, con el fin de obtener un compuesto de fórmula (XXI)

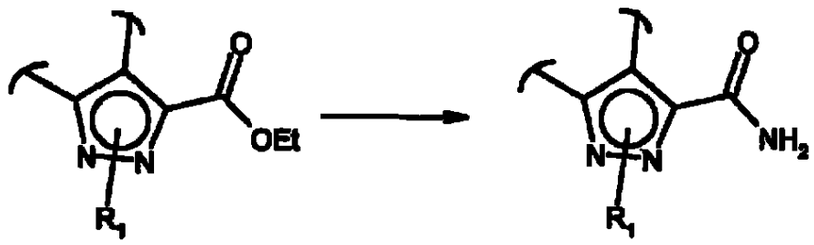


(XXI).

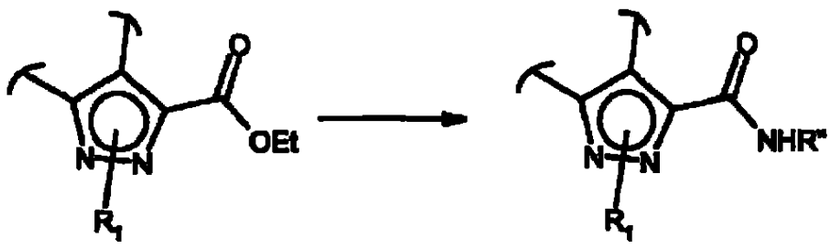
et.22) hacer reaccionar el compuesto de fórmula (XXI) con un derivado de hidrazina de fórmula (III), según la etapa (et.1) del proceso, con el fin de obtener un compuesto de fórmula (I) en donde R y R_1 son como se definieron anteriormente, X es -S- y R_2 es un grupo voluminoso; y opcionalmente convertirlos en otros derivados de fórmula (I)

25) El proceso de la reivindicación 24 en donde los compuestos de fórmula (I) siendo obtenidos en una cualquiera de las etapas (et.4a), (et.4b), (et.4c), (et.8), (et.12), (et.13), (et.18), y (et.22), son convertidos en otros compuestos de fórmula (I), dicho proceso comprende convertir estos compuestos de fórmula (I):

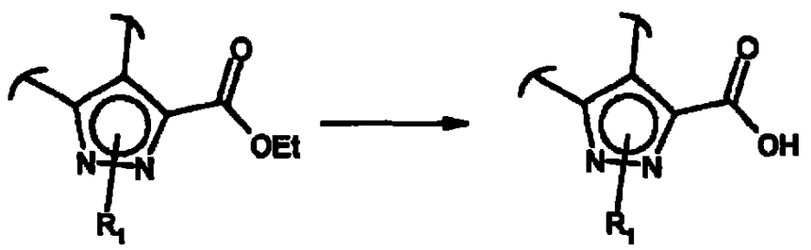
et.23) en donde R_2 es etoxi en los compuestos de fórmula (Ia) o (Ib) en donde R_2 es amino mediante el tratamiento con hidróxido de amonio



et.24) en donde R_2 es etoxi en los compuestos de fórmula (I) en donde R_2 es un grupo -NHR'', en donde R'' es como se definió anteriormente, mediante tratamiento con una amina de fórmula $R''-NH_2$ (XXII)



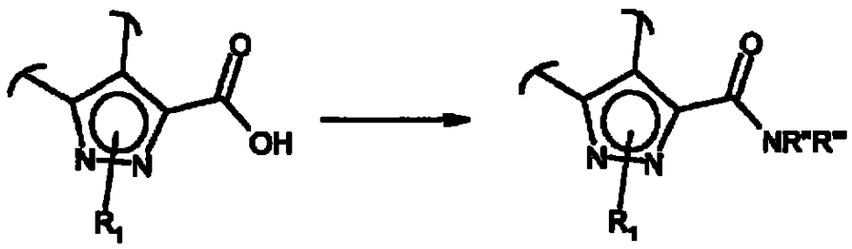
et.25) en donde R_2 es etoxi en los compuestos de fórmula (I) en donde R_2 es un grupo -OH a través de hidrólisis ácida o básica



et.26) en donde R_2 es -OH en los compuestos de fórmula (I) en donde R_2 es un grupo -NR''R''' o -N(OH)R'' y R'' y R''' son como se definió anteriormente, a través de la reacción con un derivado de fórmula (XXIII) o (XXIV)

R''R'''NH (XXIII) R''NHOH (XXIV)

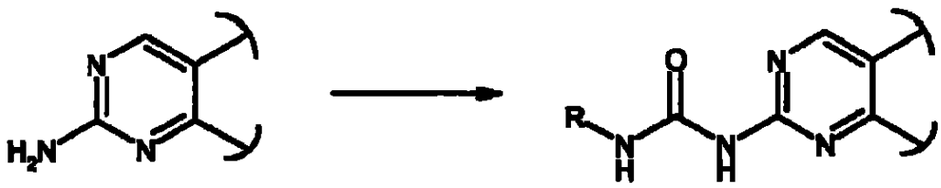
Bajo condiciones básicas y en la presencia de un agente de condensación adecuado



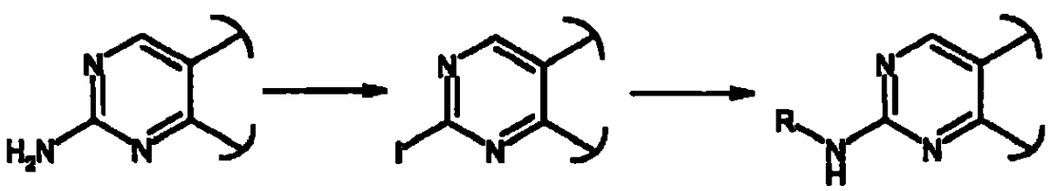
et.27) en donde R es hidrógeno y X es -NH- en los compuestos de fórmula (I) en donde R es diferente de hidrógeno, como se definió anteriormente, y X es -CONH-, a través de la reacción con un compuesto de fórmula R-COCl (XXV)



et.28) en donde R es hidrógeno y X es -NH- en los compuestos de fórmula (I) en donde R es diferente de hidrógeno, como se definió anteriormente, y X es -NH-CO-NH-, a través de la reacción con un isocianato de fórmula R-NCO (XXVI)

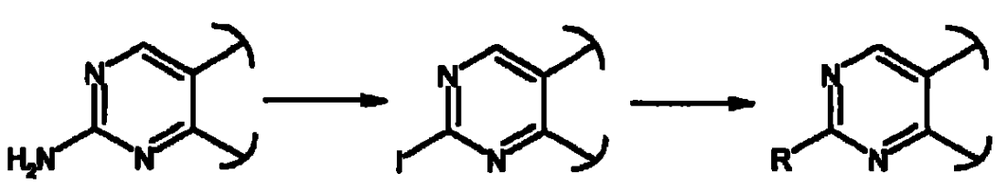


et.29) en donde R es hidrógeno y X es -NH- en los compuesto de fórmula (I) en donde R es arilo y X es -NH-, al convertir primero el grupo amino a yodo con iso-amilnitrito y diyodometano o yoduro de cesio, en la presencia de yoduro y CuI, y al reaccionar subsecuentemente el derivado de yodo con arilamina de fórmula $R-NH_2$ (XXVII), en la presencia de acetato de paladio y (2,2'-bis(difenilfosfino))-1,1'-binaftaleno (BINAP)



et.29a) en donde R es hidrógeno y X es -NH- en los compuestos de fórmula (I) en donde R es alquilo, cicloalquilo, cicloalquil-alquilo ,arilalquilo, heterociclilo, herociclilalquilo, y X es -NH-, al convertir primero el grupo amino a yodo, como se describió en la etapa previa (et.29), y al hacer reaccionar subsecuentemente el derivado de yodo con alquilo, cicloalquilo, cicloalquil-alquilo, heterociclilo o heterociclilalquilo de fórmula RNH_2 (XXVII), en donde R es como se definió allí;

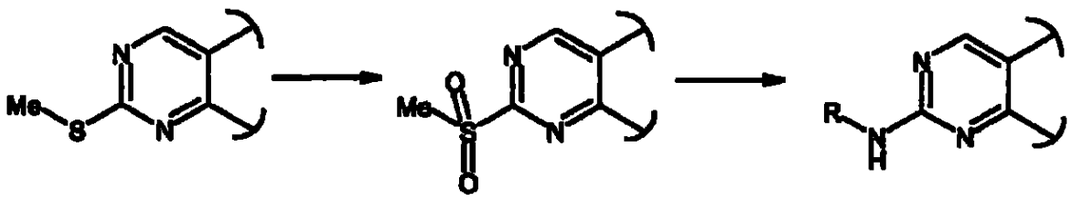
et.30) en donde R es hidrógeno y X es -NH- en los compuestos de fórmula (I) en donde R es arilo y X es un enlace sencillo, al convertir primero el grupo amino a yodo, como en la etapa anterior (et.29), y al hacer reaccionar subsecuentemente el derivado de yodo con un ácido arilborónico de fórmula $R\text{-}B(OH)_2$ (XXVIII), en la presencia de un derivado de paladio



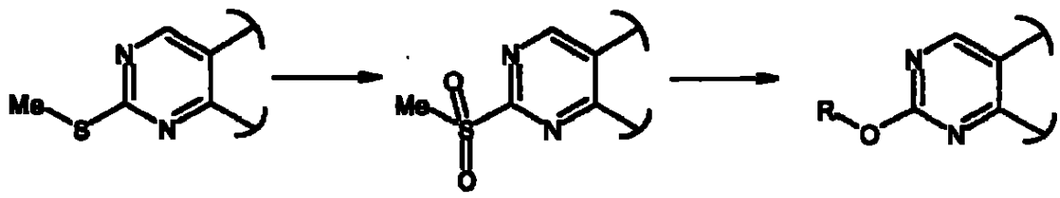
Et.31) En donde R es hidrógeno y X es -NH- en los compuestos de fórmula (I) en donde R es arilmetilo y X es un enlace sencillo, mediante la reacción con un aril-aldehido de fórmula R-CHO (XXIX) en la presencia cianoborohidruro de sodio ($NaBH_3CN$)



et.32) en donde R es metilo, y X es -S- en los compuestos de fórmula (I) en donde R es un alquilo opcionalmente sustituido, cicloalquilo, heterociclilo, cicloalquil-alquilo, arilalquilo o heterociclilalquilo, al convertir primero el grupo RS- en RSO_2- bajo condiciones oxidativas, y luego al hacer reaccionar el derivado de sulfonilo con una amina de fórmula $R-NH_2$(XXVII) en donde R es un grupo alquilo opcionalmente sustituido, cicloalquilo, heterociclilo, cicloalquil-alquilo, arilalquilo o heterociclilalquilo

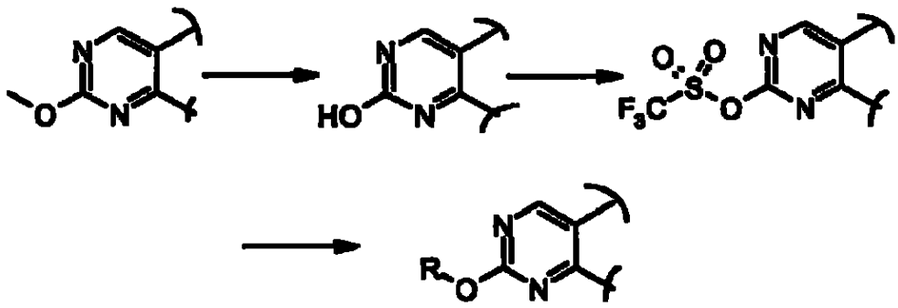


et.33) en donde R es metilo, y X es -S- en los compuestos de fórmula (I) en donde R es diferente de metilo y X es -O-, al convertir primero el grupo RS- en RSO_2- como en la etapa (et.32) y al luego hacer reaccionar el derivado de sulfonilo con un compuesto de fórmula R-OH (XXX)

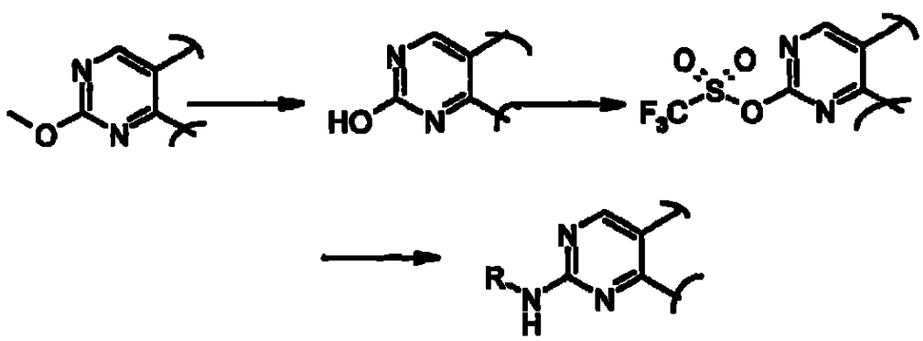


et.33a) en donde R es metilo, y X es -O- en los compuestos de fórmula (I) en donde R es diferente de metilo y X es -O-, al convertir primero el grupo MeO- en HO-, luego hacerlo reaccionar con un agente triflatante con el fin de obtener el correspondiente trifluorometansulfonato y finalmente hacerlo reaccionar con un compuesto de fórmula R-OH (XXX)

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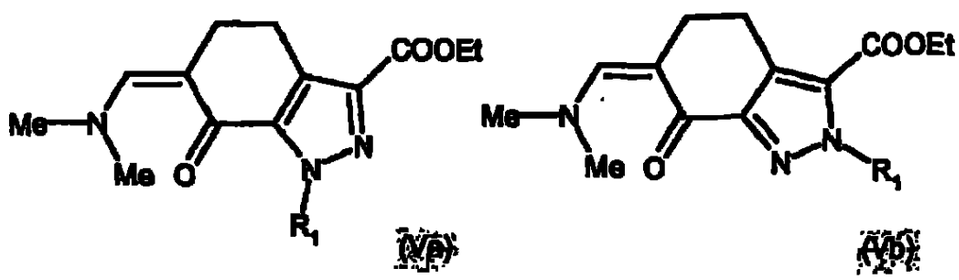
et.33b) en donde R es metilo y X es -O- se puede convertir en los compuestos de fórmula (I) en donde R es un grupo alquilo, cicloalquilo, heterociclilo, cicloalquil-alquilo, heterociclilalquilo opcionalmente sustituido, y X es -NH-, al convertir primero el grupo MeO- en HO-, luego al hacerlo reaccionar con un agente triflatante con el fin de obtener el correspondiente trifluorometansulfonato y finalmente al hacerlo reaccionar con la amina de fórmula $R-NH_2$ (XXVII) en donde R es un grupo alquilo, cicloalquilo, heterociclilo, cicloalquilalquilo, arilalquilo o heterociclilalquilo opcionalmente sustituidos



et.33c) en donde R es metilo y X es -O- se puede convertir en los compuestos de fórmula (I) en donde R es un arilo y X es-NH-, al convertir primero el grupo MeO- en -OH, luego hacerlo reaccionar con un agente triflatante con el fin de obtener trifluorometansulfonato correspondiente y finalmente hacerlo reaccionar con una amina de fórmula RNH_2 (XXVII) en donde R es un arilo opcionalmente sustituido en la presencia de acetato de paladio y BINAP;

et.34) en donde A es un grupo-$(CH2)_2$- se puede convertir en los compuestos de fórmula (I) en donde A es un grupo -CH=CH-, bajo condiciones operativas deshidrogenantes en la presencia de un catalizador Pd o Pt.

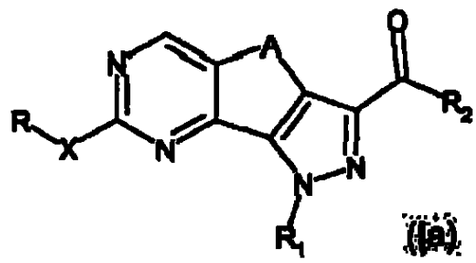
26) Un compuesto de fórmula (Va) o (Vb), como se definió en la etapa (et.3) de la reivindicación 24



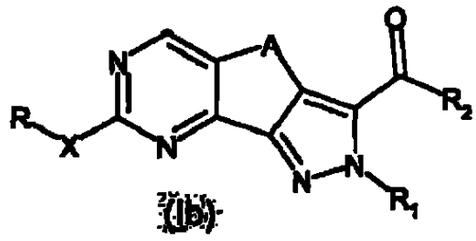
En donde R_1 es un átomo de hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6

recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo o heterociclilalquilo.

27) Una librería de dos o más compuestos de fórmula (Ia) o (Ib)



(Ia)



(Ib)

En donde R es hidrógeno o un grupo opcionalmente sustituido seleccionado de amino, alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_{10}, cicloalquil-alquilo, arilo, arilalquilo, heterociclilo o heterociclilalquilo;

X es un enlace sencillo o un radical divalente seleccionado de -NR'-, -CONR'-, -NH-CO-NH-, -O-, -S- o -SO_2-, en donde R' es hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo, heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R y R' pueden formar un grupo heteroarilo o heterociclilo de 5 a 6

miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

R_1, unido a uno cualquiera de los átomos de nitrógeno del anillo de pirazolo como por las fórmulas (Ia) o (Ib), representa un átomo de hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, en la fórmula (Ib), R_1 es un grupo divalente $-(CH_2)_n$-NH- que está ligado a R_2 en donde n es 2 o 3;

R_2 es un grupo seleccionado de -NR''R''',-N(OH)R'',-OR'' o -R'', en donde R'' y R''' son, cada uno independientemente, hidrógeno o un grupo opcionalmente sustituido seleccionado de alquilo C_1-C_6 recto o ramificado, cicloalquilo C_3-C_6, o cicloalquil-alquilo, arilo, arilalquilo, heterociclilo, o heterociclilalquilo o, junto con el átomo de nitrógeno al cual ellos están unidos, R'' y R''' pueden formar un grupo heteroarilo o heterociclilo de 5 o 6 miembros que contiene opcionalmente un heteroátomo adicional seleccionado entre N, O o S;

A es un grupo divalente seleccionado de $-CH_2-$, $-(CH_2)_2-$, $-CH_2-C(CH_3)_2-$, $-C(CH_3)_2-CH_2-$ o $-CH=CH-$; o una sal farmacéuticamente aceptable de estos.

28) Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un derivado de pirazolo-quinazolina de fórmula (Ia) o (Ib) como se definió en la reivindicación 1, y por lo menos un excipiente, portador y/o diluyente farmacéuticamente aceptable.

29) Una composición farmacéutica de acuerdo con la reivindicación 28 que además comprende uno o más agentes quimioterapéuticos.

30) Un producto o kit que comprende un compuesto de fórmula (Ia) o (Ib) como se definió en la reivindicación 1, o composiciones farmacéuticas de éste como se definió en la reivindicación 28, y uno o más agentes quimioterapéuticos, como una preparación combinada para uso secuencial, separado o simultáneo en la terapia anticáncer.

31) Un compuesto de fórmula (Ia) o (Ib) como se definió en la reivindicación 1 para uso como un medicamento.

32) Uso de un compuesto de fórmula (Ia) o (Ib) como se definió en la reivindicación 1 en la elaboración de un medicamento con actividad antitumoral.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3110MNM/ms	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2004/050612	International filing date (day/month/year) 27.04.2004	Priority date (day/month/year) 22.05.2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, C07D487/14, A61K31/519, A61P35/00

Applicant
PHARMACIA ITALIA S.P.A. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

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

Date of submission of the demand	Date of completion of this report
02.12.2004	15.04.2005

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2004/050612

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-205 as originally filed

Claims, Numbers

1-32 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2004/050612

II. Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☒ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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

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

   ☐ the entire international application,

   ☒ claims Nos. 12-23 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 12-23 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

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

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

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

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

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

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

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/EP2004/050612

Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-11,24-32
	No:	Claims	

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/EP2004/050612

Re Item III

Claims 12-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

1. PRIOR ART

Reference is made to the following documents:

D1: US 2002/119975 A1

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 resides in the basic ring system. The application relates to pyrazolo-quinazolines whereas the compounds of D1 are imidazolo-quinazolines.

3. INVENTIVE STEP

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1. It discloses imidazolo-quinazolines with anti-cancer activity. The structural difference to the present compounds is as outlined above. The problem to be solved by the present invention is seen in the provision of further quinazoline derivatives with anti-cancer activity. The prior art D1 gives structurally no information, which would motivate a man skilled in the art to arrive at the present invention.

However, the requirements of Article 33(3) PCT can presently not be considered as fulfilled. The description appears to be completely silent about the actual testing of exemplified compounds. An inventive step can only be acknowledged for subject-matter which represents such a generalisation of the examples that it is reasonable to predict

decided if the claimed compounds possess a certain activity on which the acknowledgement of an inventive step can be based.

The letter of the applicant dated 22.03.2005 contains no additional information or test results, reference is only made to the description page 2, line 26-28. From this part of the description and the argumentation of the applicant, it is still unclear which compounds have actually been tested and can be said to possess the claimed activity.

It should be noted that a reference to the description as in claim 11 should be avoided.

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TRATADO DE COOPERACIÓN DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 PCT)

Archivo de referencia del agente o solicitante

3110/MNM/ms

PARA ACCIÓN COMPLEMENTARIA

Ver Notificación de Remisión de Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)

Solicitud Internacional No.

PCT/EP2004/050612

Fecha de presentación internacional *(día/mes/año)*

27.04.2004

Fecha de Prioridad *(día/mes/año)*

22.05.2003

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

C07D487/04, C0D487/14, A61K31/519, A61P35/00

Solicitante

PHARMACIA ITALIA S.P.A. et al.

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1. Este Reporte de Examen Preliminar Internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se remite al solicitante de acuerdo con el Artículo 36.

2. Este REPORTE consiste de un total de **6** hojas, incluyendo esta hoja de portada.

   ☐ Este reporte también se acompaña por ANEXOS, es decir hojas de la descripción, reivindicaciones y/o dibujos que han sido corregidos y son la base para este reporte y/o hojas que contienen rectificaciones hechas antes a esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas de acuerdo con el PCT).

   Estos anexos consisten de un total de hojas.

3. Este Reporte contiene indicaciones relacionadas con los siguientes ítems:

   I ☒ Base del Concepto

   II ☒ Prioridad

III ☒ Concepto de sin fundamento con respecto a novedad, nivel inventivo y aplicabilidad industrial

IV ☐ Falta de unidad de invención

V ☒ Declaración motivada de acuerdo con el Artículo 66.2(a)(ii) con respecto a novedad, nivel inventivo o aplicabilidad industrial; las citaciones y explicaciones ayudan a dicha declaración

VI ☒ Ciertos documentos citados

VII ☐ Ciertos defectos en la solicitud internacional

VIII ☐ Ciertas observaciones sobre la solicitud internacional

Fecha de presentación de la petición

02.12.2004

Fecha de terminación de este reporte

15.04.2005

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REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/EP2004/050612

I. Bases del Reporte

1. Con respecto a los **elementos** de la solicitud internacional: *(reemplazo de las hojas que han sido suministradas a la Oficina de recepción en respuesta a una invitación de acuerdo con el Artículo 14 se refieren a en este reporte como "presentadas originalmente" y no se anexan a este reporte ya que ellas no contienen correcciones (Reglas 70.16 y 70.17)):*

Descripción, Páginas:

1-205 como se presentó originalmente

Reivindicaciones, Números:

1-32 presentada con telefax en 22.03.2004

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estuvieron disponibles o fueron suministrados a esta Autoridad en el idioma en el que la

solicitud internacional se presentó, a menos que se indique lo contrario de acuerdo con este ítem.

Estos elementos estuvieron disponibles o fueron suministrados a esta Autoridad en el siguiente idioma:

, que es:

☐ el idioma de una traducción suministrada para propósitos de búsqueda internacional (de acuerdo con la regla 23.1(b)).

☐ el idioma de publicación de la solicitud internacional (de acuerdo con la regla 48.3(b)).

☐ el idioma de la traducción suministrado para propósitos de examen preliminar internacional (de acuerdo con la regla 55.2 y/o 55.3).

3. Con respecto a cualquier **secuencia de ácido amino y/o nucleótido** descrito en la solicitud internacional, el concepto escrito se emitió sobre la base de la lista de secuencia:

☐ Contenida en la solicitud internacional en forma impresa

☐ Presentada junto con la solicitud internacional en forma legible por computador

- ☐ Suministrada posteriormente a esta Autoridad en forma escrita
- ☐ Suministrada posteriormente a esta Autoridad en forma escrita forma legible por computador
- ☐ La declaración de que el listado de secuencias escrito suministrado posteriormente no va más allá de la descripción en la solicitud internacional como se presentó se ha suministrado.
- ☐ La declaración de que la información registrada en forma legible por computador es idéntica al listado de secuencias escrito que se ha suministrado.

4. Las correcciones han dado como resultado la cancelación de:

☐ La descripción,	páginas:
☐ Las reivindicaciones,	Nos.:
☐ Los dibujos,	hojas:

5. ☐ Este reporte ha sido emitido como si (algunas de) las correcciones no hubieran sido hechas, ya que ellas han sido consideradas que van más allá de la descripción como se presentó, como se indicó en la casilla complementaria (Regla 70.2(c)):

(Cualquier reemplazo de hojas que contengan dichas correcciones se debe referir de acuerdo al ítem 1 y anexadas a este reporte)

REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/EP2004/050612

II. Prioridad

1. ☒ Este reporte se ha establecido como si ninguna prioridad hubiera sido reivindicado debido a falla al presentar lo requerido dentro del límite de tiempo prescrito.

   ☒ copia de la solicitud anterior cuya prioridad ha sido reivindicada.

   ☐ traducción de la solicitud anterior cuya prioridad ha sido reivindicada.

2. ☐ Este reporte se ha establecido como si ninguna prioridad hubiera sido reivindicada debido al hecho de que se ha encontrado inválida la reivindicación de prioridad.

Así para los propósitos de este concepto, la fecha de presentación internacional indicada anteriormente se considera es la fecha importante.

3. Observaciones adicionales, si es necesario.

III. Concepto de sin fundamento con respecto a novedad, nivel inventivo y aplicabilidad industrial

1. Las preguntas de si la invención reivindicada parece ser novedosa, involucrar nivel inventivo, (no ser obvia), o ser aplicable industrialmente, no se ha examinado a este respecto:

☐ La solicitud internacional completa,

☒ Las reivindicaciones No. 12-13 (aplicabilidad industrial)

Ya que:

☒ La dicha solicitud internacional, o las dichas reivindicaciones 12 - 23 se relacionan con la siguiente materia objeto que no requieren un examen preliminar (especifique):

Ver hoja separada

☐ La descripción, reivindicaciones o dibujos (*indique elementos particulares adelante*) o dichas reivindicaciones

Nos. no son claras por lo que ningún concepto importante se puede formar (especifique):

☐ Las reivindicaciones, o dichas reivindicaciones Nos. se soportan inadecuadamente por lo que ningún concepto importante se puede formar.

☐ No se ha establecido reporte de búsqueda internacional para las dichas reivindicaciones Nos.

2. Un examen preliminar internacional significativo no se puede llevara cabo debido a la falta del listado de secuencia de aminoácido y/o nucleótido para cumplir con el estándar suministrado por el Anexo C de las Instrucciones Administrativas:

☐ no se ha presentado forma escrita o no cumple con el estándar

☐ no se ha suministrado la forma legible por computador o no cumple con el estándar

V. Declaración motivada de acuerdo con el Art. 35 (2) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citaciones y explicaciones apoyan tal declaración.

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REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/EP2004/050612

Nivel Inventivo (IS)	Si:	Reivindicaciones
	No:	Reivindicaciones 1-32
Aplicabilidad Industrial	Si:	Reivindicaciones 1-11,24-32
	No:	Reivindicaciones

2. Citaciones y explicaciones

Ver hoja separada

VI. Ciertos documentos citados

1. Ciertos documentos publicados (Regla 70.10)

Y/o

2. sin descripciones escritas (Regla 70.9)

ver hoja separada

REPORTE DE EXAMEN

PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/EP2004/050612

Re ítem III

Las reivindicaciones 12-23 se relacionan con la materia objeto considerada por esta autoridad para ser cubierta por las provisiones de la regla 67.1(IV) PCT. Por con siguiente, no se formulará ningún concepto con respecto a la aplicabilidad industrial de la materia de objeto de estas reivindicaciones (articulo 34(4)(a)(I) PCT).

Re ítem V

1 TÉCNICA ANTERIOR

Se hace referencia a los siguientes documentos:

D1: US 2002/119975 A1

2 NOVEDAD

La materia de objeto de las reivindicaciones se consideran novedosa (Artículo 33(2)PCT). La diferencia estructural esencial entre los compuestos o reivindicados y aquellos de D1 residen en el sistema de anillo básico. La solicitud se relaciona con pirazolo-quinazolinas mientras que los compuestos de D1 se relacionan con imidazolo-quinazolina.

3 NIVEL INVENTIVO

El documento D1 se considera es el estado de la técnica más cercano a la materia objeto de la reivindicación 1. Esta describe imidazolo-quinazolinas con actividad anticancerígena. La diferencia estructural de los compuestos presentes es como se destacó anteriormente. El problema a ser resuelto por la presente invención se ve en la provisión de derivados de quinazolina adicionales con actividad anticancerígena. El D1 de la técnica anterior no da información estructural, que pudiera motivar a un hombre experto en la técnica a alcanzar la presente invención. Sin embargo, los requerimientos del artículo 33(3)PCT pueden actualmente no ser considerados como cumplidas. La descripción parece ser completamente silente acerca del ensayo actual de los compuestos ejemplificados. Un nivel inventivo solo puede ser reconocido para la materia u objeto

que representa tal una generalización de los ejemplos que es razonable para predecir

decidido si los compuestos reivindicados poseen una cierta actividad en la cual se reconoce un nivel inventivo en el que se pueda basar.

La carta del solicitante fechada 22.03.2005 no contiene información adicional o resultados de ensayo, solo hace referencia a la página 2 línea 26-28. Desde esta parte de la descripción y el argumento del solicitante, todavía no es claro que compuestos actualmente han sido ensayados y se puede decir que poseen la actividad reivindicada.

Se debe anotar que una referencia a la descripción como en la reivindicación 11 se debe evitar.

646.

Folio 648 y 649

Extracto Publicado

Folios 646 y 647

~~150~~ 647

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05118410 00000000 Folios: 650
Fecha (AMD): 2005-11-22 16:57:52
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 0020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	(X)	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(X)	( )
Descripción de la invención.	(X)	( )
Dibujos de ser estos pertinentes.	(X)	( )
Comprobante de Pago de las tasas establecidas. (X)		
COMPLETA (X)	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable:

Fecha: Noviembre 22 de 2005

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO
Apoderado(a) y/o Representante de
PHARMACIA ITALIA S.P.A.

REFERENCIA	Radicación No.	05 118410
	Solicitud internacional	EP2004/050612
	Fecha inicio fase nacional	22/12/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	1472

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 10 FEB. 2006
adpal