OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-099656- -00000-0000
Fecha: 2007-09-25 16:37:30 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 609

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL **P2007/000156**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GLAXO GROUP LIMITED
Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN
Nacionalidad o Domicilio: BRITANICA
Lugar de Constitución: INGLATERRA
Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número _____

(3) **REPRESENTANTE O APODERADO**

Nombre: J. IAN RAISBECK
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 Fax: 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual _____
Número 79.376.996 Btá
TP 135.799

(4) **INVENTOR (ES) (72)**

Nombre: 1. JAMES FRANCIS CALLAHAN, 2. ZEHONG WAN, 3. HONGXING YAN WILSON
Dirección: 709 Swedeland Road, King of Prussia, Pennsylvania 19406, Estados Unidos de América.
Nacionalidad o Domicilio: 1. Estadounidense, 2 y 3 China

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2006/010792 Fecha 24 Marzo 2006
Publicación Internacional No. WO 2006/104889 Fecha 5 Octubre 2006

(6) **Título (54)** COMPUESTOS NOVEDOSOS

(7) **Clasificación Internacional (51)** **A61K 31/519, C07D 487/02** ; A61P 11/00

(8) **Prioridad**
SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 25, 2005	60/665.347

(9) **Comprobante de pago No: 07 – 75.609** **Fecha 18 septiembre 2007**

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-018.321
- [x] Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la Regla 4.17 del PCT
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o 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.
- [x] Otros. Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-099656--00000-0000
Fecha: 2007-09-25 12:37:30 Dep: 2020 NUECREACIONI
Tra: 1 PATENTEYI Eve: 378 FASENACIONALI
ACTO: PRESENTACION Folios: 609

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 75,609
FECHA : SEPTIEMBRE 18 DE 2007

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO POPULAR	050-00110-6	68290537	18/09/2007	7,259,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

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

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Ingle
Resolución No. 2117 del 7 O.

DE PINNA
NOTARIES

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada **"GLAXO GROUP LIMITED"**, Sociedad legalmente constituída y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debiday suficientemente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy ece de agosto del año dos mil tres.

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

SCRIVENER NOTARIES

DE PINNA
35 Piccadilly London W1J OLJ
Telephone:+44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0068 DX No. 48521 Piccadilly 2

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
   a été signé par

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

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

Certified/Attesté

5. at London/à Londres

6. the/le **14 August 2003**

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

8. Number/sous No **G229474**

9. Stamp:
   timbre:

10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

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

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

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

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England

Certification of Facsimile Transmission
I hereby certify that this paper is being facsimile transmitted to
The International Bureau of WIPO on the date shown below.
Irene M. Mulligan June 1, 2006
Signature/Date

PU61344 **Fax # 41-22-740-1435**

International Application No.:	PCT/US065/10792
International Filing Date:	26 March 2006
Priority Date Claimed:	25 March 2005
Applicant:	Glaxo Group Limited, et al
Title of Invention:	Novel Compounds

INTERNATIONAL BUREAU OF WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

REQUEST TO INCLUDE INVENTORS' DECLARATIONS

Pursuant to Rules 26*ter* and 92*bis*, please include with the International Application the enclosed declarations of applicant/inventors. They are as follows: Entitlement to Apply for and be Granted a Patent; Entitlement to Claim Priority; and Inventorship (Sheet Nos. 4-8).

Please charge any additional fees which may be required by the addition or replacement of these declarations, or credit any overpayment, to Deposit Account No. 19-2570.

Respectfully submitted,

Dara L. Dinner
Attorney for Applicant
Registration No. 33,680

GlaxoSmithKline
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Telephone: 610-270-5017
Fax: 610-270-5090

Box No. V DESIGNATION OF STATES

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for thegrant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection

☐ KR Republic of Korea **is not designated** for any kind of national protection

☐ RU Russian Federation **is not designated** for any kind of national protection

(The check boxes above may be used to exclude (irrevocably) the designations concerned in ortder to avoic the ceasing of the effect, under the national law, of an earlier application from which priority is claimed. See the notes to Box no. V as to the consequences of such national law provisiona in these and certain other states.)

Box No. VI PRIORITY CLAIM

Filing Date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country or member of WTO	Where earlier application is: regional application:* regional Office	Where earlier application is: international application: receiving Office
item (1) 25 March 2005 (25.03.05)	60/665347	item (1) United States of America		
item (2)				
item (3)				

☐ **Further priority claims are indicated in the Supplemental Box.**

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

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

**Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)).....*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

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

ISA/US

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

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

			Number of declarations
☐	Box No. VIII(i)	Declaration as to the identity of the inventor	:
☒	Box No. VIII(ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	: 3
☒	Box No. VIII(iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	: 3
☒	Box No. VIII(iv)	Declaration of inventorship (only for the purposes of the designation the United States of America)	: 3
☐	Box No. VIII(v)	Declaration as to non-prejudicial disclosures or exceptions to lack novelty	:

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

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

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application,

GLAXO GROUP LIMITED is entitled to apply for and be granted a patent by virtue of the following:

an assignment from

CALLAHAN, James Francis of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 20 April 2006;

WAN, Zehong of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 20 April 2006; and

YAN, Hongxing of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 21 April 2006.

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

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

Box No. VIII(iii) DECLARATION: ENTTILEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII(i) to (v) (in general) and the specific Notes to Box No. VIII(iii) and 51*bis*.1(a)(iii)

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):

in relation to this international application,
GLAXO GROUP LIMITED is entitled to claim priority of earlier application No. 60/665347 filed in the United States of America by virtue of the following:

an assignment from CALLAHAN, James Francis of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 20 April 2006;

an assignment from WAN, Zehong of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 20 April 2006; and

an assignment from YAN, Hongxing of 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America to GLAXO GROUP LIMITED dated 21 April 2006.

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

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

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

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

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

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

This application is directed to international application No. PCT/US06/10792 (if furnishing declaration pursuant to Rule 26*ter*).

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

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

Prior Applications:_____

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

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

Name: James Francis CALLAHAN

Residence: 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: United States of America

Inventor's Signature: James Francis Callahan Date: 20-Apr-2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Zehong WAN

Residence: 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: China

Inventor's Signature: Zehong WAN Date: 20-Apr-2006
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent.)
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

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

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

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

Name: Hongxing YAN

Residence: 709 Swedeland Road, King of Prussia, Pennsylvania 19406, United States of America

Mailing Address: GlaxoSmithKline, Corporate Intellectual Property - UW2220, P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Citizenship: China

Inventor's Signature: _____ Date: 21-Apr-2006

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

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 October 2006 (05.10.2006)

PCT

(10) International Publication Number
WO 2006/104889 A2

(51) International Patent Classification:
A61K 31/519 (2006.01) *C07D 487/02* (2006.01)

(21) International Application Number:
PCT/US2006/010792

(22) International Filing Date: 24 March 2006 (24.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/665,347 25 March 2005 (25.03.2005) US

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CALLAHAN, James Francis** [US/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **WAN, Zehong** [CN/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US). **YAN, Hongxing** [CN/US]; 709 Swedeland Road, King Of Prussia, Pennsylvania 19406 (US).

(74) Agents: **DINNER, Dara** et al.; GlaxoSmithKline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King Of Prussia, Pennsylvania 19406-0939 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *without international search report and to be republished upon receipt of that report*

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

WO 2006/104889 A2

(54) Title: NOVEL COMPOUNDS

(57) Abstract: Novel substituted 1,5,7-trisubstituted-354-dihydro-pyriinido[4,5-(flpyrimidin- 2-(2H)-one compounds and compositions, and their use in therapy as CSBP/RK/p38 kinase inhibitors.

Attorney Docket No.: PU61344

NOVEL COMPOUNDS

Summary of the Invention

This invention relates to novel 1,5,7-trisubstituted-3,4-dihydro-pyrimido[4,5-*d*]pyrimidin-2-[*1H*]-one compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of certain diseases and conditions.

Background of the Invention

Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e. g. protein tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phospholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J. C. Cell, **80**, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being tyrosine kinases and serine / threonine kinases, depending upon whether the enzyme phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T., Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

Three major related intracellular pathways, the mitogen-activated kinases, or MAPKs, are now understood to transduce signals from many extracellular stimuli such as environmental stress, infectious agents, cytokines and growth factors. The MAPKs modulate the activity of numerous cell functions such as translocation and activation of transcription factors that control transcription of effector molecules such as cytokines, COX-2, iNOS; the activity of downstream kinases that effect translation of mRNAs; and cell cycle pathways through transcription or modification of enzymes. One of these three major pathways is the p38 MAPK pathway, which refers in most cell types to the isoform p38a which is ubiquitously expressed. The role of p38 in a multitude of functions, particularly related to inflammatory response has been elucidated using selective p38 inhibitors in numerous in vitro and in vivo studies. These functions have been extensively reviewed and a summary can be found in Nature Reviews [Kumar, S. Nature Rev. Drug Discovery, 2:717 (2003)]

Extracellular stimuli such as those described above are generated in a number of chronic diseases which are now understood to have a common underlying

pathophysiology termed inflammation. An environmental insult or local cell damage activates cellular response pathways, including but not limited to p38; local cells then generate cytokines and chemokines, in turn recruiting lymphocytes such as neutrophils and other granulocytes. In a secondary response, the consequences include recruitment of additional lymphocytes such as additional phagocytic cells or cytotoxic T cells, and ultimately the adaptive immune response is initiated through activation of T cells. It is not currently fully understood how this acute inflammatory response becomes a chronic response leading to diseases such as rheumatoid arthritis (RA), athersclerosis, chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), etc. Nevertheless, the features of inflammation are recognized to contribute to a large number of chronic diseases and pathways such as the p38 pathway are accepted to contribute to the initiation of inflammatory diseases.

For example, atherosclerosis is regarded as a chronic inflammatory disease, which develops in response to injury of the vessel wall and is characterized by the complex development of an occlusive and prothrombotic atheroma. The pathogenesis of this lesion generally involves endothelial dysfunction (reduced bioavailable NO), adhesion molecule expression, adhesion and infiltration of leukocytes, cytokine and growth factor generation, accumulation of foam cells, expansion of extracellular lipid and matrix, activation of matrix metalloproteases (MMPs) and proliferation of vascular smooth muscle cells.

The discovery of p38 (initially termed CSBP, now p38; the isoforms p38α and p38β are the targets of the compounds described) provided a mechanism of action of a class of anti-inflammatory compounds for which SK&F 86002 was the prototypic example. These compounds inhibited IL-1 and TNF synthesis in human monocytes at concentrations in the low uM range [Lee, *et al.*, Int. J. Immunopharmac. 10(7), 835(1988)] and exhibited activity in animal models which are refractory to cyclooxygenase inhibitors [Lee; *et al.*, Annals N. Y. Acad. Sci., **696**, 149(1993)].

The mechanism by which stress signals (including bacterial and viral infection, pro-inflammatory cytokines, oxidants, UV light and osmotic stress) activate p38 is through activation of kinases upstream from p38 which in turn phosphorylate p38 at threonine 180 and tyrosine 182 resulting in p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp27 and other substrates. Additional downstream substrates known to be phosphorylated by p38 include kinases (Mnk1/2, MSK1/2 and PRAK) and transcription factors (CHOP, MEF2, ATF2 and CREB). While many of the signaling pathways required for transduction of stress stimuli remain unknown it appears clear that many of the substrates for p38 listed above are involved.

[Cohen, P. Trends Cell Biol., 353-361(1997) and Lee, J. C. et al, Pharmacol. Ther. vol. 82, nos. 2-3, pp. 389-397, 1999]. There is also emerging evidence that p38 is involved in modulation of the activity of the NF-kB signaling pathway through a role in histone phosphorylation or acetylation, or through reduction of transcription competence of the NF-kB complex [Saccini, S. Nature Immunol., 3: 69-75, (2002); Carter, AB et al J Biol Chem 274: 30858-63 (1999)]. Finally, a role for p38 in generation of response to IFNs through activation by the Type I IFN receptor has been described [Platanias, Pharmacol. Therap. 98:129-142 (2003)]. Activation of p38 is involved in the transcriptional regulation of IFN sensitive genes through modification of specific transcription factors binding to promotor elements in these genes. Direct phosphorylation of STATs by p38 has not been conclusively demonstrated.

In addition to inhibiting IL-1 and TNF upregulation in response to inflammatory stimuli, p38 kinase inhibitors (e.g., SK&F 86002 and SB-203580) are effective in a number of different cell types in decreasing the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF, RANTES and COX-2. Inhibitors of p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that p38 is involved not only cytokine synthesis in response to stress, but also in propagating the consequent cytokine signaling [CSBP/P38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are important inflammatory cytokines produced by a variety of cells, such as monocytes, macrophages, and smooth muscle cells. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Evidence also links IL-1

activity to diabetes and pancreatic ß cells [review of the biological activities which have been attributed to IL-1 Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985)].

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic obstructive pulmonary disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

Inflammatory diseases are also marked by increases in IL-6 and C-reactive protein (CRP), both of which are sensitive to inhibition by p38 inhibitors. IL-6 stimulation of CRP production is directly inhibited by p38 inhibitors in human vascular endothelial cells, and CRP is produced by hepatocytes in response to IL-6. CRP is considered a major risk factor for cardiovascular disease [Circulation 2003.107: 363-369] and may be a significant independent risk factor for chronic obstructive pulmonary disease [Circulation 2003. 107:1514-1519]. IL-6 is also upregulated in endometriosis [Bedaiwy et al., 2002, Human Reproduction 17:426-431; Witz, 2000, Fertility and Sterility 73: 212-214].

Interleukin-8 (IL-8) and RANTES are chemotactic factors produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, epithelial cells, neutrophils and T cells. Chemokine production is induced by pro-inflammatory stimuli such as IL-1, TNF, or lipopolysachharide (LPS), or viral infection. IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, which may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions such as chronic obstructive pulmonary disease associated with an increase in IL-8 production would benefit by compounds which are suppressive of IL-8 production. RANTES is produced by cells such as epithelial cells and airway smooth muscle in response to infection or cytokine stimulation. Its main chemoattraction is for T cell subtypes and blood-borne monocytes.

IL-1, TNF and other cytokines affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important as critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

In addition to the involvement of p38 signaling in the production of IL-1, TNF, IL-8, IL-6, GM-CSF, COX-2, collagenase and stromelysin, signal transduction via CSBP/p38 is required for the effector functions of several of these same pro-inflammatory proteins plus many others. For example, growth factors such as VEGF, PDGF, NGF signal through surface receptors which in turn activate cellular signaling pathways including p38 MAPK [Ono, K. and Han, J., Cellular Signalling, **12** 1-13 (2000); Kyriakis, JM and Avruch, J. Physiol Rev **81**: 807-869 (2001)]. TGFχ, a key molecule in the control of inflammatory response, also activates p38 as a consequence of engagement of the TGFβ receptor. The involvement of CSBP/p38 in multiple stress-induced signal transduction pathways provides additional rationale for the potential utility of CSBP/p38 in the treatment of diseases resulting from the excessive and destructive activation of the immune system, or chronic inflammation. This expectation is supported by the potent and diverse activities described for CSBP/p38 kinase inhibitors [Badger, *et al.*, J. Pharm. Exp. Thera. **279** (3): 1453-1461.(1996); Griswold, *et al*, Pharmacol. Comm. 7, 323-229 (1996); Jackson, *et al.*, J. Pharmacol. Exp. Ther. **284**, 687- 692 (1998); Underwood, *et al.*, J. Pharmacol. Exp. Ther. **293**, 281- 288 (2000); Badger, *et al.*, Arthritis Rheum. **43**, 175 -183 (2000)].

Chronic inflammation is also characterized by ongoing remodeling and repair of affected tissue, leading in some cases to excess fibrotic tissue. A role for p38 MAPK in fibrosis is supported by findings that this enzyme mediates signaling of transforming growth factor beta (TGF-β) on markers and proteins of fibrosis. For example, it has been shown that TGF-β increases the kinase activity of p38 MAPK through the TGF-β activated kinase TAK-1 (Hanafusa et al., 1999, J. Biol. Chem. **274**:27161-27167). Furthermore, the p38 inhibitor SB-242235 inhibited the TGF-β-induced increases in fibronectin and thrombospondin (Laping et al., 2002, Molec. Pharmacol. **62**:58-64). These results show that p38 MAPK is a key signaling intermediate for the effect of the pro-fibrotic cytokine TGF-β on components of the extracellular matrix and markers of fibrosis.

P38 also plays a role in directing survival and apoptosis of cells in response to various stimuli. Both survival and apoptosis can be p38 regulated depending on the stimulus and the cell type [Morin and Huot, Cancer Research. **64**:1893-1898 (2004)]. For example, TGF-beta can stimulate apoptosis in murine hepatocytes through

activation of gadd45b, a protein involved in cell-cycle control, in a p38 mediated process [Yoo et al, J. Biol. Chem. 278:43001-43007, (2003)]. In a different response pathway, UV-stress can activate p38 and trigger apoptosis of a damaged cell. P38 has also been shown to promote survival of lymphocytes in response to stress, including neutrophils and CD8+ T cells.

There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting the CSBP/p38/RK kinase. The present invention is directed to such novel compounds which are inhibitors of p38 kinase.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof; and pharmaceutical compositions comprising a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

This invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

This invention also relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa),

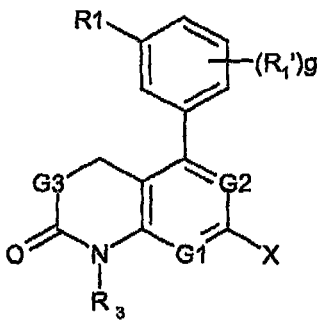
(IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

This invention also relates to a method of inhibiting the production of IL-6 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

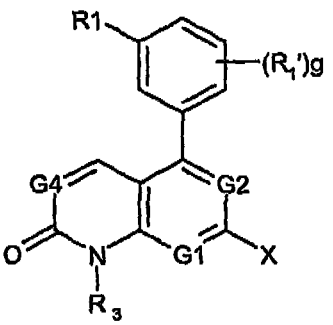
This invention also relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

This invention also relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (IX) and (IXa), (A), (A1), (B), and (B1), and a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Accordingly, the present invention provides for a compound of Formula (I) and (Ia) having the structure:



(I)



(Ia)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{2}" is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein R_{2}" is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR4'R14', excluding the moieties SR_5 being SNR4'R14', $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

R9' is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{10}' is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a

heterocyclylC1-4 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R13 is independently selected at each occurrence from hydrogen, C1-4 alkyl, halo-substituted C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C3-7 cycloalkyl, C3-7cycloalkylC1-4 alkyl, C5-7 cycloalkenyl, C5-7cycloalkenyl C1-4 alkyl, aryl, arylC1-4 alkyl, heteroaryl, heteroarylC1-4 alkyl, heterocyclyl, or a heterocyclylC1-4 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

Rd and Rd' are each independently selected at each occurrence from hydrogen, C1-4 alkyl, C3-6 cycloalkyl, C3-6 cycloalkylC1-4alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or Rd and Rd' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; or

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

DETAILED DESCRIPTION OF THE INVENTION

The novel compound of Formula (I) are discussed in greater detail described below.

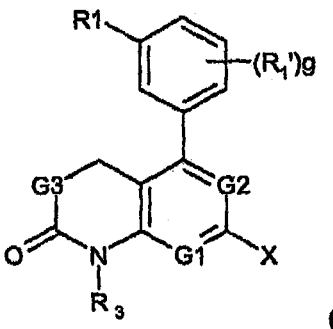
The present invention is directed to novel compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi),), (A), (A1), (B), (B1), (VI), (VIa), (VIII) and (VIIIa), (IX) and (IXa), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. As will be readily recognized, the difference between compounds of Formula (I) and (Ia) lies in

unsaturation of the ring system. The difference between compound of Formula (I) and (Ia) and compounds of Formula (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), (A), (A1), (B), (B1), (VI), (VIa), (VIII) and (VIIIa) lies in ring substitution of the R_1 substituent on the aryl (or heteroaryl moiety when G5 and/or G6, etc are nitrogen), and the ring position of the nitrogen(s) for the pyridyl or pyrimidine pharmacophore where applicable. It is recognized that the ring position numbering may change due to the nitrogen's in the pharmacophore ring and or in the ring that the R1 substituent is attached in.

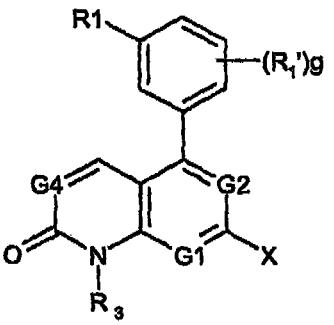
The respective R_1, R_1', R_2, R_3, R_X, X and R_3, etc., terms are the same for both groups within the formulas themselves, for instance, in Formula (I) and (Ia), and except for the additional G5/G6/G7/G8 terms, applicable across all formulas herein. For purposes herein, everything applicable to Formula (I) is also applicable to Formula (Ia) unless otherwise indicated, and for the remaining compounds of Formula (II) and (IIa), etc. unless specified otherwise.

It is recognized that for compounds of Formula (I) and (Ia) wherein G_3 and G_4 are both nitrogen and G_1 and G_2 are both nitrogen, the ring system is considered to be a 1,5,7-trisubstituted-3,4-dihydro-pyrimido[4,5-*d*]pyrimidin-2-[*1H*]-one.

Compounds of Formula (I) and (Ia) are further represented by the structure:



(I)



(Ia)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

R_1' is independently selected at each occurrence from hydrogen, halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})R_h$ NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted; or R_q and $R_{q'}$ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally C_{1-10} alkyl;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and

wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently at each occurrence from C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R10')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_{e'}$, $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}$alkyl $NR_eR_{e'}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_{e'}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_{e'}$, $(CR_{10}R_{20})_nN(R10')C(Z)R_6$, $(CR_{10}R_{20})_nN(R10')C(=N(R10'))\ NR_eR_{e'}$, $(CR_{10}R_{20})_nC(=NOR6)\ NR_eR_{e'}$,

$(CR_{10}R_{20})_nOC(Z)\ NR_eR_e'$, $(CR_{10}R_{20})_nN(R10')C(Z)\ NR_eR_e'$, or $(CR_{10}R_{20})_nN(R10')C(Z)OR_7$; or wherein

R_2 is the moiety $(CR_{10}R_{20})_q'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q'C(A_1)(A_2)(A_3)$;

R_2' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and

wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently at each occurrence from C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R10'')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkylNR_eR_e'$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_e'$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R10')C(Z)R_6$, $(CR_{10}R_{20})_nN(R10')C(=N(R10'))\ NR_eR_e'$, $(CR_{10}R_{20})_nC(=NOR_6)\ NR_eR_e'$, $(CR_{10}R_{20})_nOC(Z)\ NR_eR_e'$, $(CR_{10}R_{20})_nN(R10')C(Z)\ NR_eR_e'$, or $(CR_{10}R_{20})_nN(R10')C(Z)OR_7$;

R_2'' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and

wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently at each occurrence from C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R10')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkyl\ NR_eR_e'$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_e'$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R10')C(Z)R_6$, $(CR_{10}R_{20})_nN(R10')C(=N(R10'))\ NR_eR_e'$, $(CR_{10}R_{20})_nC(=NOR_6)\ NR_eR_e'$, $(CR_{10}R_{20})_nOC(Z)\ NR_eR_e'$, $(CR_{10}R_{20})_nN(R10')C(Z)\ NR_eR_e'$, or $(CR_{10}R_{20})_nN(R10')C(Z)OR_7$; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, and

wherein these moieties are all optionally substituted one or more times, independently at each occurrence from hydrogen, halogen, nitro, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7}cycloalkenyl, C_{5-7}cycloalkenylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_{16}R_{26}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_{16}R_{26}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_{16}R_{26}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R_{10'}))NR_{16}R_{26}$, $(CR_{10}R_{20})_nOC(Z)NR_{16}R_{26}$, $(CR_{10}R_{20})_nN(R_{10''})C(Z)NR_{16}R_{26}$, or $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or heteroaryl C_{1-4} alkyl; or the R_4 and R_{14} together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and

wherein the C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl C_{1-4} alkyl moieties, and the R_4 and R_{14} cyclized ring are optionally substituted, 1 to 4 times, independently at each occurrence, by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; SR_5; $S(O)R_5$; $S(O)_2R_5$; $C(O)R_j$; $C(O)OR_j$; $C(O)NR_4'R_{14'}$; $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$; $(CR_{10}R_{20})_nN(R_{10'})C(Z)$ $NR_dR_{d'}$; $NR_4'C(O)C_{1-10}$alkyl; $NR_4'C(O)$aryl; $NR_4'R_{14'}$; cyano; nitro; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; an unsubstituted or substituted aryl, or arylC_{1-4} alkyl; an unsubstituted or substituted heteroaryl, or heteroaryl C_{1-4} alkyl; an unsubstituted or substituted heterocyclic, or heterocyclic C_{1-4} alkyl, and wherein these aryl, heterocyclic and heteroaryl containing moieties are substituted one to two times independently at each occurrence by halogen; C_{1-4} alkyl, hydroxy; hydroxy substituted C_{1-4} alkyl;

C_{1-4} alkoxy; $S(O)_m$alkyl; amino, mono & di-substituted C_{1-4} alkyl amino, or CF_3;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ can cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$;

$R_{4''}$ and $R_{14''}$ are independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4''}$ and $R_{14''}$ together with the nitrogen to which they are attached, cyclize to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

R_6 is independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl, wherein each of these moieties, excluding hydrogen are optionally substituted;

R_7 is independently selected at each occurrence from C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, or heteroarylC_{1-6}alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_8 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted;

R_9 is independently selected at each occurrence from hydrogen, $C(Z)R_6$, optionally substituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted aryl-C_{1-4} alkyl;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl,

arylC1-4 alkyl, heteroaryl, heteroarylC1-4 alkyl, heterocyclyl, or heterocyclylC1-4 alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted;

R13 is independently selected at each occurrence from hydrogen, C1-4 alkyl, halo-substituted C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C3-7 cycloalkyl, C3-7cycloalkylC1-4 alkyl, C5-7 cycloalkenyl, C5-7cycloalkenyl C1-4 alkyl, aryl, arylC1-4 alkyl, heteroaryl, heteroarylC1-4 alkyl, heterocyclyl, or a heterocyclylC1-4 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R15 and R25 are independently selected at each occurrence from hydrogen, C1-4 alkyl, C3-7 cycloalkyl, C3-7 cycloalkylC1-4alkyl, aryl, or aryl-C1-4 alkyl, heterocyclic, heterocyclic C1-4 alkyl heteroaryl or heteroaryl C1-4 alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted; or R15 and R25 together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9; and

wherein these moieties , excluding hydrogen, are optionally substituted 1 to 4 times, independently at each occurrence from halogen; hydroxy; hydroxy substituted C1-10alkyl; C1-10 alkoxy; halosubstituted C1-10 alkoxy; halosubstituted C1-4 alkyl; SR5, S(O)R5, S(O)2R5; C(O)Rj; C(O)ORj; C(O)NR4'R14'; NR4'C(O)C1-10alkyl; NR4'C(O)aryl; NR4'R14'; cyano; nitro; C1-10 alkyl; C3-7cycloalkyl; C3-7cycloalkyl C1-10 alkyl; halosubstituted C1-10 alkyl; aryl, aryl C1-4 alkyl, heterocyclic, heterocyclic C1-4 alkyl, heteroaryl, or hetero C1-4 alkyl, and wherein these aryl, heterocyclic, and heteroaryl containing moieties may also be substituted one to two times independently at each occurrence by halogen, C1-4 alkyl, hydroxy, hydroxy substituted C1-4 alkyl, C1-10 alkoxy, S(O)m C1-4 alkyl, amino, mono & di-substituted C1-4 alkylamino, C1-4 alkyl, or CF3;

R16 and R26 are each independently selected at each occurrence from hydrogen, or C1-4 alkyl; or the R16 and R26 together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

R21' and R31' are independently selected at each occurrence from hydrogen or C1-4 alkyl, or R21' and R31' together with the nitrogen to which they are attached

cyclize to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety; and

which moieties may all be optionally substituted 1 to 4 times independently at each occurrence from halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; OR_8, SR_5, $S(O)R_5$, $S(O)_2R_5$; $C(O)R_j$; $C(O)OR_j$; $C(O)NR_{15}R_{25}$; cyano; nitro; $NR_{15}R_{25}$; -Z'-$(CR_{10}R_{20})$s-Z'-, C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; an optionally substituted aryl or arylalkyl, an optionally substituted heteroaryl and heteroarylC_{1-10} alkyl, and an optionally substituted heterocyclic and heterocyclicC_{1-10} alkyl, and wherein these aryl, heteroaryl and heterocyclic containing moieties may also be substituted one to two times independently at each occurrence from halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_mC_{1-4}$ alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl, or the R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9'; and

wherein the R_d and R_d' moieties which are C_{1-4} alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4} alkyl, and the R_d and R_d' cyclized ring are substituted, 1 to 4 times, independently at each occurrence by halogen; halosubstituted C_{1-4} alkyl; hydroxy; hydroxy substituted C_{1-4}alkyl; C_{1-4} alkoxy; halosubstituted C_{1-4} alkoxy; S(O)mRf; C(O)Rj; C(O)ORj; $C(O)NR_4'R_{14}'$; $NR_4'C(O)C_{1-4}$alkyl; $S(O)_2NR_4'R_{14}'C_{1-4}$ alkyl; $NR_4'R_{14}'S(O)_2C_{1-4}$ alkyl; or $NR_4'R_{14}'$;

R_e are R_e' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety; or R_e and R_e' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and

wherein each of these moieties, excluding hydrogen, may be substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; amino, mono & di-substituted C_{1-4} alkyl amino; $S(O)_mR_{f'}$; $C(O)R_j$; $C(O)ORj$; $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$; $(CR_{10}R_{20})_nN(R_{10'})C(Z)NR_dR_{d'}$; $C(O)NR_{4'}R_{14'}$; $NR_{4'}C(O)C_{1-10}$alkyl; $NR_{4'}C(O)$aryl; cyano; nitro; C_{1-10} alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; aryl, aryl C_{1-4} alkyl, heterocyclic, heterocyclicC_{1-4} alkyl, heteroaryl, or heteroC_{1-4}alkyl, and wherein these aryl, heterocyclic, and heteroaryl containing moieties may be optionally substituted one to two times independently at each occurrence by halogen, C_{1-4} alkyl, hydroxy, hydroxy substituted C_{1-4} alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3;

R_f is independently selected at each occurrence from C_{1-10}alkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, heteroaryl C_{1-10}alkyl, heterocyclic, or a heterocyclic C_{1-10}alkyl moiety, and wherein these moieties may all be optionally substituted;

$R_{f'}$ is independently selected at each occurrence from hydrogen, C_{1-10}alkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, heteroaryl C_{1-10}alkyl, heterocyclic, heterocyclic C_{1-10}alkyl or $NR_{4'}R_{14'}$; and wherein these moieties, excluding hydrogen, and $NR_{4'}R_{14'}$, may be optionally substituted;

R_j is independently selected at each occurrence from hydrogen, C_{1-4}alkyl, aryl, aryl C_{1-4}alkyl, heteroaryl, heteroaryl C_{1-4}alkyl, heterocyclic, or a heterocyclic C_{1-4}alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted;

g is 0, or integer having a value of 1, 2, 3, or 4;

n is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

n' is independently selected at each occurrence from 0 or an integer having a value of 1 to 10;

m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

s is independently selected at each occurrence from an integer having a value of 1, 2, or 3;

t is an integer having a value of 2 to 6;

Z is independently selected at each occurrence from oxygen or sulfur;

Z' is independently selected at each occurrence from oxygen, or sulfur; and

a pharmaceutically acceptable salt thereof, solvate or physiologically functional derivative thereof.

Suitably, for compounds of Formula (I), and (Ia), and the remaining formulas described herein R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$.

In one embodiment of the invention, R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_v R_b$, or $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$. In another embodiment of the invention R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_v R_b$.

Suitably, $R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$.

In one embodiment, $R_{1'}$ is independently selected at each occurrence from halogen, C_{1-4} alkyl, or halo-substituted-C_{1-4} alkyl. In another embodiment, $R_{1'}$ is independently selected at each occurrence from fluorine, chlorine, methyl, or CF_3.

Suitably, g is 0 or an integer having a value of 1, 2, 3, or 4. In one embodiment of the invention, g is 0, 1 or 2.

For compounds of Formula (I) and (Ia), when $R_{1'}$ is substituted on a phenyl ring in the ortho position, and a second $R_{1'}$ moiety is also substituted on the ring, then preferably the second substitution is not in the other ortho position. Suitably, the phenyl ring is substituted in the 2-position and if a second substituent is present, in the 3-position with the R_1 moiety in the 5-position. Alternatively, the $R_{1'}$ moiety may be in the other ortho 2-position and the R_1 moiety in the 3-position, which will change the ring position numbering.

Suitably, R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, C_{3-5} cycloalkylC_{1-4}alkyl, or the R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$, and wherein the R_d and $R_{d'}$ moieties which are C_{1-4} alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4} alkyl, and the R_d

and $R_{d'}$ cyclized ring are optionally substituted, 1 to 4 times, independently at each occurrence by halogen; halosubstituted C_{1-4} alkyl; hydroxy; hydroxy substituted C_{1-4}alkyl; C_{1-4} alkoxy; halosubstituted C_{1-4} alkoxy; S(O)mRf; C(O)Rj; C(O)ORj; $C(O)NR_{4'}R_{14'}$, $NR_{4'}C(O)C_{1-4}$alkyl; $S(O)_2NR_{4'}R_{14'}C_{1-4}$ alkyl; $NR_{4'}R_{14'}S(O)_2C_{1-4}$ alkyl; or $NR_{4'}R_{14'}$.

Suitably $R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl.

Suitably, Z is independently selected at each occurrence from oxygen or sulfur.

Suitably, v is 0 or an integer having a value of 1 to 2.

Suitably, v' is 0 or an integer having a value of 1 or 2.

Suitably, R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4} alkyl.

Suitably, $R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4} alkyl.

Suitably, R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl, and wherein these moieties, excluding hydrogen, may be optionally substituted.

Suitably, R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted and wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times by halogen; halosubstituted C_{1-4} alkyl; C_{1-4} alkyl; hydroxy; hydroxy substituted C_{1-4}alkyl; C_{1-4}alkoxy; halosubstituted C_{1-4} alkoxy; S(O)mC_{1-4} alkyl; -C(O), C(O)C_{1-4} alkyl; or $NR_{21'}R_{31'}$.

Suitably, $R_{21'}$ and $R_{31'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{21'}$ and $R_{31'}$ together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, nitrogen, or sulfur.

Suitably R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a

heterocyclylC_{1-10} alkyl moiety, which moieties, excluding hydrogen, are all optionally substituted.

The R_b moieties, excluding hydrogen, may be optionally substituted, one or more times, preferably 1 to 4 times independently at each occurrence by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; halosubstituted C_{1-10} alkoxy; OR_8, such as methoxy, ethoxy or phenoxy; SR_5, $S(O)R_5$, $S(O)_2R_5$, such as methyl thio, methylsulfinyl or methyl sulfonyl; $C(O)R_j$; $C(O)OR_j$; $C(O)NR_{4''}R_{14''}$; cyano; nitro; $NR_{15}R_{25}$; -Z'-$(CR_{10}R_{20})$s-Z'; C_{1-10}alkyl; C_{3-7}cycloalkyl or a C_{3-7}cycloalkyl C_{1-10} alkyl group, such as cyclopropyl, or cyclopropyl methyl, or cyclopropylethyl, etc.; halosubstituted C_{1-10} alkyl, such CF_2CF_2H, CH_2CF_3, or CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylC_{1-10}alkyl, such as benzyl or phenethyl; an optionally substituted heterocyclic or heterocyclic C_{1-10}alkyl, or an optionally substituted heteroaryl or heteroaryl C_{1-10}alkyl, and wherein these aryl, heteroaryl, and heterocyclic containing moieties may also be substituted one to two times independently at each occurrence by halogen, hydroxy, hydroxy substituted C_{1-4} alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

The moiety -Z'-$(CR_{10}R_{20})$s-Z' forms a cyclic ring, such as a dioxalane ring.

Suitably Z' is independently selected at each occurrence from oxygen, or sulfur.

Suitably, s is independently selected at each occurrence from an integer having a value of 1, 2, or 3.

Suitably, R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH.

Suitably, $R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$. Suitably, when $R_{4'}$ and $R_{14'}$ cyclize to form an optionally substituted ring, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

Suitably, $R_{4''}$ and $R_{14''}$ are each independently selected at each occurrence from hydrogen or C_{1-10} alkyl, or $R_{4''}$ and $R_{14''}$ can cyclize together with the nitrogen to which they are attached to form an optionally substituted 5 to 7 membered ring which optionally contains an additional heteroatom selected from oxygen, sulfur

or $NR_{9'}$. Suitably, when $R_{4''}$ and $R_{14''}$ cyclize to form an optionally substituted ring, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, morpholine, and thiomorpholine (including oxidizing the sulfur).

Suitably, R_f is independently selected at each occurrence from hydrogen, C_{1-10}alkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, heteroaryl C_{1-10}alkyl, heterocyclic, or a heterocyclic C_{1-10}alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted.

Suitably, R_j is independently selected at each occurrence from C_{1-10}alkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, heteroaryl C_{1-10}alkyl, heterocyclic, or a heterocyclic C_{1-10}alkyl moiety, which moieties may all be optionally substituted.

Suitably, when R_b is an optionally substituted C_{1-10}alkyl, the moiety includes but is not limited to a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, isobutyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, heptyl, 2-methylpropyl; a halosubstituted alkyl, such as 2,2,2-trifluroethyl, trifluromethyl, 2-fluoroethyl; a cyano substituted alkyl, such as cyanomethyl, cyanoethyl; an alkoxy, thio or hydroxy substituted alkyl, such as 2-methoxy-ethyl, 2-hydroxy propyl or serinol, or an ethylthioethyl.

In an alternative embodiment, when R_b is an optionally substituted C_{1-10}alkyl the moiety is a methyl, ethyl, n-propyl, isopropyl, t-butyl, n-butyl, or 2,2-dimethylpropyl or 2-hydroxy propyl group.

Suitably, when R_b is an optionally substituted heteroaryl, or heteroarylalkyl, the heteroaryl containing moiety includes but is not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil, indolyl, isoindolyl, indazolyl, indolizinyl, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl, and phthalazinyl.

In one embodiment, when R_b is an optionally substituted heteroaryl it is a 1,3-thiazol-2-yl or 5-methyl-1,3-thiazol-2-yl, isoquinolinyl, thiophene, e.g. a 3-thiophene, indol-5-yl, pyridinyl, e.g. a pyridin3-yl, or pyridine-4-yl, indazolyl, benzothiazolyl, 2-methyl-1,3-benzothiazol-5-yl, 1*H*-imidazol-4-yl or 1*H*-imidazol-4-ylethyl. Further to this, the heteroaryl ring is an optionally substituted thiazolyl, pyridyl, or thiophene ring. Preferably, R_b is an optionally substituted 1,3-thiazol-2-yl.

Suitably, when R_b is an optionally substituted heterocyclic, or heterocyclicalkyl, the heterocyclic containing moiety includes but is not limited to tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including

oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety). In one embodiment, the heterocyclic, or heterocyclic alkyl group is pyrazol-3-yl, 4-morpholino, unsubstituted and substituted 2-furanyl, or 2-furanylmethyl, 2-thienyl or 2-thienylmethyl, tetrahydro-2H-pyran-4yl, or tetrahydro-2H-pyran-4yl methyl, tetrahydro-2-furanyl, or tetrahydro-2-furanylmethyl.

Suitably, when R_b is an optionally substituted aryl or arylalkyl moiety, the aryl containing moiety is unsubstituted or substituted independently at each occurrence one or more times by halogen, alkyl, cyano, OR_8, SR_5, $S(O)_2R_5$, $C(O)R_j$, $C(O)OR_j$, $-Z'-(CR_{10}R_{20})s-Z'$, halosubstituted C_{1-10} alkyl, or an optionally substituted aryl.

In one embodiment, R_b is a phenyl, or napthylene, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,3-difluorphenyl, 2,4-diflurophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 2-methyl phenyl, 3-methylphenyl, 4-methylphenyl, 6-methyl phenyl, 2-methyl phenyl, 3-amino phenyl, 3,4-dimethyl phenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, benzyl, phenethyl, phenylpropyl, 2,3-difluoro-benzyl, 3,5-difluoro-benzyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamindo-2-methylphenyl, or 3-phenyloxyphenyl, 4-phenyloxyphenyl, 4-(1-piperidinylsulfonyl)-phenyl, or 3-(aminocarbonyl)phenyl.

In another embodiment, R_b is a phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-diflurophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-chloro-4-fluorophenyl, 4-methyl-3-fluorophenyl, 4-trifluorophenyl, 2-methylphenyl, 3-methylphenyl, 4-ethoxyphenyl, 4-methoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, 4-thiomethylphenyl, 4-acetylphenyl, 4-dimethylaminophenyl, biphenyl, 4'-fluorobiphenyl, 4-sulfonamindo-2-methylphenyl, 3-phenyloxyphenyl, benzyl, or phenethyl. Further to this R_b is a 4-fluorophenyl.

Suitably, when R_b is an optionally substituted cycloalkyl or cycloalkyl alkyl moiety, the moiety is a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, or a cyclopentylmethyl. In another embodiment, R_b is a cyclopropyl or cyclopropylmethyl group.

In another embodiment, R_b is C_{1-10} alkyl, heteroaryl, or aryl, all optionally substituted.

In another embodiment, R_b is hydrogen, or an optionally substituted alkyl.

In one embodiment of the invention R_b is an alkyl, such as propyl or isopropyl; heteroaryl, such as a thiazolyl; an aryl, such phenyl, or 4-F phenyl; an arylalkyl, or a cycloalkylalkyl moiety, all optionally substituted. In another embodiment, R_b is alkyl, heteroaryl, or aryl, all optionally substituted.

Suitably, m is independently selected at each occurrence from 0 or an integer having a value of 1 or 2.

For each of the integer variables where appropriate, e.g. n, n', m, q', s, t, or v', etc. they are independently chosen at each occurrence.

Suitably, R_8 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted independently at each occurrence, 1 to 4 times, by halogen; halosubstituted C_{1-4} alkyl; C_{1-4} alkyl; C_{3-5}cycloalkyl; C_{3-5}cycloalkyl C_{1-4}alkyl; halosubstituted C_{1-4} alkyl; hydroxy; hydroxy substituted C_{1-4}alkyl; C_{1-4}alkoxy; halosubstituted C_{1-4} alkoxy; S(O)mC_{1-4} alkyl; -C(O), C(O)C_{1-4} alkyl; $NR_{21'}R_{31'}$; or an aryl or aryl C_{1-4} alkyl, and wherein these aryl containing moieties may also be substituted one to two times independently at each occurrence, by halogen, hydroxy, hydroxy substituted alkyl, C_{1-4} alkoxy, $S(O)_mC_{1-4}$alkyl, amino, mono & di-substituted C_{1-4} alkylamino, C_{1-4} alkyl, or CF_3.

Suitably, R_{15} and R_{25} are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, or aryl-C_{1-4} alkyl, heteroaryl or heteroaryl C_{1-4} alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted; or R_{15} and R_{25} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9; and wherein these moieties are optionally substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; SR_5, $S(O)R_5$, $S(O)_2R_5$; $C(O)R_j$; $C(O)OR_j$; $C(O)NR_{4'}R_{14'}$; $NR_{4'}C(O)C_{1-10}$alkyl; $NR_{4'}C(O)$aryl; $NR_{4'}R_{14'}$; cyano; nitro; C_{1-10} alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; aryl, arylC_{1-4} alkyl, heteroaryl, or heteroC_{1-4} alkyl, heterocyclic and

heterocyclicC_{1-4} alkyl and wherein these aryl, heterocyclic and heteroaryl containing moieties may also be substituted one to two times independently at each occurrence by halogen, C_{1-4} alkyl, hydroxy, hydroxy substituted C_{1-4} alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

Suitably, R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or heteroaryl C_{1-4} alkyl; or the R_4 and R_{14} together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen.

The R_4 and R_{14} moieties, excluding hydrogen, of C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, aryl, aryl-C_{1-4} alkyl, heteroaryl and heteroaryl C_{1-4} alkyl moieties, heterocyclic, or heterocyclic C_{1-4} alkyl moieties, and the R_4 and R_{14} cyclized ring are optionally substituted, one or more times, preferably 1 to 4 times, independently at each occurrence, by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; SR_5; $S(O)R_5$; $S(O)_2R_5$; $C(O)R_j$; $C(O)OR_j$; $C(O)NR_4'R_{14}'$; $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$; $(CR_{10}R_{20})_nN(R_{10}')C(Z)\ NR_dR_{d'}$; $NR_4'C(O)C_{1-10}$alkyl; $NR_4'C(O)$aryl; $NR_4'R_{14}'$; cyano; nitro; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; C_{1-10} alkyl substituted one or more times by an optionally substituted aryl; an unsubstituted or substituted aryl, or arylC_{1-4} alkyl; an unsubstituted or substituted heteroaryl, or heteroaryl C_{1-4} alkyl; an unsubstituted or substituted heterocyclic, or heterocyclic C_{1-4} alkyl, and wherein these aryl, heterocyclic and heteroaryl containing moieties are substituted one to two times independently at each occurrence by halogen; C_{1-4} alkyl, hydroxy; hydroxy substituted C_{1-4} alkyl; C_{1-4} alkoxy; $S(O)_m$alkyl; amino, mono & di-substituted C_{1-4} alkyl amino, or CF_3.

Suitably, when R_4 and R_{14} together with the nitrogen cyclize to form an optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, diazepine, morpholine, and thiomorpholine (including oxidizing the sulfur).

Suitably, R_6 is independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or a heteroarylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen may be optionally substituted independently at each occurrence, one or more times, suitably 1 to 2 times, by halogen; hydroxy; hydroxy substituted

C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; S(O)m alkyl; C(O); $NR_{4'}R_{14'}$; C_{1-10} alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; an unsubstituted or substituted aryl or aryl C_{1-4} alkyl, an unsubstituted or substituted heteroaryl or heteroaryl C_{1-4} alkyl, or a unsubstituted or substituted heterocyclic or heterocyclic C_{1-4} alkyl, and wherein these aryl, heterocyclic, or heteroaryl containing moieties may be substituted independently at each occurrence, one or two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

Suitably, R_9 is independently selected at each occurrence from hydrogen, $C(Z)R_6$, optionally substituted C_{1-10} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl. These alkyl, aryl and arylalkyl moieties may be optionally substituted 1 or 2 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; S(O)m alkyl; -C(O); $NR_{4'}R_{14'}$; C_{1-10} alkyl, C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; an aryl or aryl C_{1-4} alkyl, and wherein these aryl containing moieties may also be substituted one or two times independently by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_mC_{1-4}$ alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

Suitably, R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties may be optionally substituted one ore more times, suitably 1 to 4 times, independently at each occurrence by hydrogen, halogen, nitro, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10} alkyl, C_{5-7}cycloalkenyl, C_{5-7}cycloalkenylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_{16}R_{26}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_{16}R_{26}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_{16}R_{26}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R_{10'}))NR_{16}R_{26}$, $(CR_{10}R_{20})_nOC(Z)NR_{16}R_{26}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)\ NR_{16}R_{26}$, or $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$.

In one embodiment, the R_3 moieties are optionally substituted 1 to 4 times, independently at each occurrence by halogen, nitro, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4}alkynyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-4} alkyl, C_{5-6}cycloalkenyl, C_{5-6}cycloalkenylC_{1-4} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nNHS(O)_2R_7$, $(CR_{10}R_{20})_nS(O)_2NR_{16}R_{26}$, $(CR_{10}R_{20})_nNR_{16}R_{26}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nC(Z)R_6$,

$(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, or $(CR_{10}R_{20})_nC(Z)NR_{16}R_{26}$.

In one embodiment the R_3 moieties are optionally substituted independently, one or more times, suitably 1 to 4 times, independently at each occurrence by the R_3 optional substitutent is independently selected from halogen, C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nNR_{16}R_{26}$, or halo-substituted C_{1-10} alkyl.

In another embodiment the optional subsitutents are independently selected at each occurrence from halogen, C_{1-10} alkyl, hydroxy, C_{1-10} alkoxy, cyano, nitro, amino, or halosubstituted C_{1-10} alkyl. In another embodiment, the R_3 substituents are selected independently from halogen, such as fluorine, chlorine, bromine or iodine, or C_{1-10} alkyl, such as methyl.

In one embodiment the R_3 moieties are an optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-7}cycloalkylalkyl, or optionally substituted aryl. In another embodiment, the R_3 moiety is an optionally substituted C_{1-10} alkyl, or an optionally substituted aryl. In another embodiment, R_3 is an optionally substituted phenyl. Further to this embodiment, R_3 is a phenyl ring substituted one or more times by independently at each occurrence by fluorine, chlorine, hydroxy, methoxy, amino, methyl, or trifluoromethyl. Preferably, R_3 is a 2,6-difluorophenyl.

Suitably, in one embodiment when R_3 is an aryl moiety, it is an optionally substitued phenyl ring. The phenyl is optionally substituted one or more times, independently at each occurrence, suitably 1 to 4 times by halogen, C_{1-4} alkyl, or halo-substituted-C_{1-4} alkyl. The phenyl ring may be substituted in the 2, 4, or 6-position, or di-substituted in the 2,4- position or 2,6-position, such as 2-fluoro, 4-fluoro, 2,4-difluoro, 2,6-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position, such as 2,4,6-trifluoro.

Suitably, R7 is independently selected at each occurrence from C_{1-6}alkyl, aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, or *heteroaryl*C_{1-6}alkyl; and wherein each of these moieties may be optionally substituted one or two times independently at each occurrence, by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; S(O)m alkyl; C(O); $NR_{4'}R_{14'}$; C_{1-10} alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkylC_{1-10} alkyl; halosubstituted C_{1-10} alkyl; an aryl or aryl C_{1-4} alkyl moiety, and wherein these aryl containing moieties may also be substituted independently at each occurrence, one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

Suitably, R_{16} and R_{26} are each independently selected at each occurrence from hydrogen, or C_{1-4} alkyl; or the R_{16} and R_{26} together with the nitrogen which they are attached form an unsubstituted or substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9'.

Suitably, n is 0, or an integer having a value of 1 to 10.

Suitably, X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_nN(R_{11})S(O)mR_{2'}$, $(CH_2)_nN(R_{11})C(O)R_{2'}$, $(CH_2)_nNR_4R_{14}$, $(CH_2)_nN(R_{2'})(R_{2''})$, or $N(R_{10'})R_hNH\text{-}C(=N\text{-}CN)NRqRq'$.

In one embodiment of the invention X is $N(R_{10'})R_hNH\text{-}C(=N\text{-}CN)NRqRq'$.

Suitably, X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$. In one embodiment of the invention, X_1 is $N(R_{11})$, or O.

Suitably, R_h is selected from an optionally substituted C_{1-10} alkyl, $\text{-}CH_2\text{-}C(O)\text{-}CH_2\text{-}$, $\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}$, $\text{-}CH_2\text{-}C(O)N(R_{10'})CH_2\text{-}CH_2\text{-}$, $\text{-}CH_2\text{-}N(R_{10'})C(O)CH_2\text{-}$, $\text{-}CH_2\text{-}CH(OR_{10'})\text{-}CH_2$, $\text{-}CH_2\text{-}C(O)O\text{-}CH_2\text{-}CH_2\text{-}$, or $\text{-}CH_2\text{-}CH_2\text{-}O\text{-}C(O)CH_2\text{-}$.

Suitably, R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring of 5 to 7 members, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulphur.

Suitably, R_{11} is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl.

Suitably, R_2 is independently selected from hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted C_{3-7} cycloalkyl, optionally substituted C_{3-7}cycloalkylalkyl, optionally substituted aryl, optionally substituted arylC_{1-10}alkyl, optionally substituted heteroaryl, optionally substituted heteroarylC_{1-10} alkyl, optionally substituted heterocyclic, optionally substituted heterocyclylC_{1-10}alkyl moiety; or R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$.

Suitably q' is 0, or an integer having a value of 1 to 6.

The R_2 moieties, excluding hydrogen, may be optionally substituted one or more times, preferably 1 to 4 times, independently at each occurrence by C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl,

C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_{e'}$, $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}alkylNR_eR_{e'}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_{e'}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)\ NR_eR_{e'}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R_{10'}))\ NR_eR_{e'}$, $(CR_{10}R_{20})_nC(=NOR_6)\ NR_eR_{e'}$, $(CR_{10}R_{20})_nOC(Z)\ NR_eR_{e'}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)\ NR_eR_{e'}$, or $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$.

Suitably, R_e and $R_{e'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, which moieties may be optionally substituted; or R_e and $R_{e'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen; and wherein each of these moieties, including the cyclized ring and excluding hydrogen, may be substituted 1 to 4 times, independently at each occurrence by halogen; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy; C_{1-10} alkyl; halosubstituted C_{1-4} alkyl; $S(O)mR_{f'}$; $C(O)R_j$; $C(O)ORj$; $(CR_{10}R_{20})_nN(R10')C(Z)OR_7$; $(CR_{10}R_{20})_nN(R_{10'})C(Z)NR_dR_{d'}$; $C(O)NR_{4'}R_{14'}$; $NR_{4'}C(O)C_{1-10}$alkyl; $NR_{4'}C(O)$aryl; cyano; nitro; $NR_{4'}R_{14'}$; C_{1-10} alkyl; C_{3-7}cycloalkyl; C_{3-7}cycloalkyl C_{1-10} alkyl; halosubstituted C_{1-10} alkyl; aryl, arylC_{1-4}alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl, or hetero C_{1-4} alkyl, and wherein these aryl, heterocyclic or heteroaryl containing moieties may be optionally substituted one to two times independently at each occurrence by halogen, C_{1-4} alkyl, hydroxy, hydroxy substituted C_{1-4} alkyl, C_{1-10} alkoxy, $S(O)_m$alkyl, amino, mono & di-substituted C_{1-4} alkyl amino, C_{1-4} alkyl, or CF_3.

Suitably, $R_{f'}$ is independently selected at each occurrence from hydrogen, C_{1-10}alkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, heteroaryl C_{1-10}alkyl, heterocyclic, heterocyclic C_{1-10}alkyl or $NR_{4'}R_{14'}$;, and wherein these moieties, excluding hydrogen, and $NR_{4'}R_{14'}$, may be optionally substituted.

When X is R_2 and R_2 is an optionally substituted heterocyclic or heterocyclic alkyl, the heterocyclic containing moiety is suitably selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl,

pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

In one embodiment, R_2 is an optionally substituted piperidinyl or piperazinyl ring.

In another embodiment, when R_2 is an optionally substituted heterocyclic or heterocyclic alkyl ring the ring is substituted one or mores times independently by an optionally substituted heterocyclic, heterocyclic alkyl, aryl, arylalkyl, alkyl, $(CR_{10}R_{20})_nNR_eR_{e'}$, or $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$. The second heterocyclic ring is suitably selected from an optionally substituted tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Suitably, the second heterocyclic ring is selected from morpholino, piperidine, or pyrrolidinyl.

In one embodiment, R_2 is a 4-amino-1-piperidinyl, 1,1-dimethylethyl)oxy]-carbonyl}amino)-1-piperidinyl, 4-methyl-1-piperazinyl, 4-ethyl-1-piperazinyl, 4-propyl-1-piperazinyl, 4-butyl-1-piperazinyl, 4-(methylamino)-1-piperidinyl, 1,1-dimethylethyl-4-piperidinyl}methylcarbamate, 4-phenyl-1-piperazinyl, 1,4'-bipiperidin-1'-yl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-methyl-1,4'-bipiperidin-1'-yl, 4-(4-morpholinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, or 4-methylhexahydro-1H-1,4-diazepin-1-yl.

Suitably, $R_{2'}$ is independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently, at each occurrence, by C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenylC_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10'})S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_{e'}$, $(CR_{10}R_{20})_nNR_eR_{e'}C_{1-4}alkylNR_eR_{e'}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_{e'}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_{e'}$, $(CR_{10}R_{20})_nN(R_{10'})C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10'})C(=N(R10'))NR_eR_{e'}$, $(CR_{10}R_{20})_nC(=NOR_6)\ NR_eR_{e'}$,

$(CR_{10}R_{20})_nOC(Z)\ NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)\ NR_eR_e'$, or $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$.

In one embodiment, when X is $(CH_2)_nN(R_2')(R_2'')$, one of R_2', or R_2'' is hydrogen, or methyl.

In one embodiment, when R_2' is an optionally substituted heterocyclic or heterocyclylC_{1-10} alkyl the heterocyclic containing moiety is substituted one or more time independently by C_{1-10} alkyl, aryl, heteocyclic, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$, or $(CR_{10}R_{20})_nC(Z)OR_6$. More specifically, methyl, ethyl, $NHC(O)O\text{-}CCH_3$, $N(CH_3)C(O)O\text{-}CCH_3$, amino, methylamino, dimethylamino, phenyl, piperidine, pyrrolidine, 1-ethylpropyl, 4-methyl-1,4'-bipiperidin-1'-yl, 1,4'-bipiperidin-1'-yl, morpholino,

In one embodiment, when X is $(CH_2)_nN(R_2')(R_2'')$, R_2' is an optionally substituted C_{1-10} alkyl, cycloalkyl, heterocyclic, heterocyclyl C_{1-10} alkyl, heteroarylalkyl. Suitably, when R_2' is an optionally substituted cycloalkyl it is a cyclohexyl ring. In one embodiment the cyclohexyl ring is optionally substituted one or more times by $(CR_{10}R_{20})_nNR_eR_e'$.

Suitably, when R_2' is an optionally substituted heterocyclic, or a heterocyclylC_{1-10} alkyl, the ring is selected from tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, diazepine, hexahydro-1-H-azepine, morpholino or thiomorpholino (including oxidized versions of the sulfur moiety). Preferably, the ring is a piperidine, piperazine, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, morpholino, hexahydro-1-H-azepine ring. In one embodiment, the rings are substituted one or more times, suitably 1 to 4 times, independently by C_{1-10} alkyl, aryl, arylalkyl, $(CR_{10}R_{20})_nNR_eR_e'$, or $(CR_{10}R_{20})_nN(R10')C(Z)OR_7$.

In one embodiment, $(CH_2)_nN(R_2')(R_2'')$ is 1-(phenylmethyl)-4-piperidinamine, 2-[4-(phenylmethyl)-1-piperazinyl]ethylamine, 2-(1-piperidinyl)ethylamine, 2-(1-methyl-2-pyrrolidinyl)ethylamine, 1-[(phenylmethyl)-3-pyrrolidinyl]amine, 3-[(1-pyrrolidinyl)propyl]amine, 3-[(hexahydro-1H-azepin-1-yl)propyl]amine, (1-methyl-4-piperidinyl)amine, 3-[(4-morpholinyl)propyl]amine, 3-[(2-oxo-1-pyrrolidinyl)propyl]-amine, 2-[(4-morpholinyl)ethyl]amine, 2-[(1-pyrrolidinyl)ethyl]-amine, or [(1-ethyl-2-pyrrolidinyl)methyl]amino.

In one embodiment when X is $(CH_2)_nN(R_2')(R_2'')$, and R_2' is an optionally substituted C_{1-10} alkyl, the alkyl is substituted one or more times independently by

$(CR_{10}R_{20})_nNR_eR_e'$ or $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkylNR_eR_e'$. In one embodiement R_e and and R_e' are independently an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl. Preferably, $(CH_2)_nN(R_2')(R_2'')$ is 3-(dimethylamino)propyl(methyl)amine, 3-(diethylamino)propylamine, propylamine, (2,2-dimethylpropyl)amine, (2-hydroxypropyl)amino, 2-(dimethylamino)ethylamine, 2-(dimethylamino)ethyl(methyl)amine, 3-(dimethylamino)propylamine, 2-(dimethylamino)ethyl(methyl)amine, 3-(diethylamino)propylamine, 2-(methylamino)ethylamine, [(1-methylethyl)amino]ethylamine, 3-(diethylamino)propylamine, 3-(dibutylamino)propylamine, 3-[(1-methylethyl)amino]propylamine, 3-(1,1-dimethylethyl)aminopropylamine, 3-(dimethylamino)-2,2-dimethylpropylamine, 4-(diethylamino)-1-methylbutylamine, or 3-[[3-(dimethylamino)propyl]-(methyl)amino]propyl(methyl)amine.

Suitably R_2'' is selected from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted 1 to 4 times, independently at each occurrence, by C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenyl C_{1-10} alkyl, halogen, -C(O), cyano, nitro, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, heterocyclylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10}')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_eR_e'$, $(CR_{10}R_{20})_nNR_eR_e'C_{1-4}alkylNR_eR_e'$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_eR_e'$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10}')C(=N(R_{10}'))\ NR_eR_e'$, $(CR_{10}R_{20})_nC(=NOR_6)\ NR_eR_e'$, $(CR_{10}R_{20})_nOC(Z)NR_eR_e'$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)NR_eR_e'$, or $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$; or wherein R_2'' is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

Suitably, t is an integer having a value of 2 to 6.

Suitably, q is 0 or an integer having a value of 1 to 10.

Suitably, A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl.

Suitably, A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl.

Suitably, A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl.

The A_1, A_2, and A_3 C_{1-10} alkyl moieties may optionally substituted one or more times independently at each occurrence, preferably from 1 to 4 times, with halogen, such as chlorine, fluorine, bromine, or iodine; halo-substituted C_{1-10}alkyl, such as CF_3, or CHF_2CF_3; C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7}cycloalkenyl, C_{5-7} cycloalkenylC_{1-10}alkyl, $(CR_{10}R_{20})_nOR_6$, $(CR_{10}R_{20})_nSH$, $(CR_{10}R_{20})_nS(O)_mR_7$, $(CR_{10}R_{20})_nN(R_{10}')S(O)_2R_7$, $(CR_{10}R_{20})_nNR_4R_{14}$, $(CR_{10}R_{20})_nCN$, $(CR_{10}R_{20})_nS(O)_2NR_4R_{14}$, $(CR_{10}R_{20})_nC(Z)R_6$, $(CR_{10}R_{20})_nOC(Z)R_6$, $(CR_{10}R_{20})_nC(Z)OR_6$, $(CR_{10}R_{20})_nC(Z)NR_4R_{14}$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)R_6$, $(CR_{10}R_{20})_nN(R_{10}')C(=N(R_{10}'))NR_4R_{14}$, $(CR_{10}R_{20})_nOC(Z)NR_4R_{14}$, $(CR_{10}R_{20})_nN(R_{10}')C(Z)NR_4R_{14}$, or $(CR_{10}R_{20})_nN(R_{10}')C(Z)OR_7$.

In another embodiment of the present invention, X is R_2, and R_2 is $(CR_{10}R_{20})_q'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q'C(A_1)(A_2)(A_3)$. In a further embodiment, q' is 0.

In another embodiment when R_2 is the moiety $(CR_{10}R_{20})_q'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, q' is 0, X_1 is nitrogen, q is 0 or 1, A_1 is an optionally substituted heterocyclic or heterocyclic alkyl, and A_2 is an optionally substituted aryl. More specifically, R_2 is 2-phenyl-2-(1-pyrrolidinyl)ethyl]amino, or 1-phenyl-2-(1-pyrrolidinyl)ethyl]amino.

In one embodiment of the invention, one or more of the A_1, A_2 and A_3 moieties are substituted with $(CR_{10}R_{20})_nOR_6$. In another embodiment of the invention, the R_6 substituent in $(CR_{10}R_{20})_nOR_6$ is hydrogen.

In yet another embodiment of the present invention, X is R_2 and R_2 is $(CR_{10}R_{20})_q'C(A_1)(A_2)(A_3)$, such as $CH(CH_2OH)_2$, or $C(CH_3)(CH_2OH)_2$; or wherein R_2 is $(CR_{10}R_{20})_q'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$ and q' is 0, and the moiety is $X_1(CR_{10}R_{20})qCH(CH_2OH)_2$, or $X_1(CR_{10}R_{20})qC(CH_3)(CH_2OH)_2$; in another embodiment X_1 is oxygen or nitrogen.

In one embodiment of the present invention X is R_2, OR_2', $(CH_2)_nNR_4R_{14}$, or $(CH_2)_nN(R_2')(R_2'')$.

In another embodiment X is $S(O)_mR_2'$, $(CH_2)_nNR_4R_{14}$, or $(CH_2)_nN(R_2')(R_2'')$.

In yet another embodiment, X is $(CH_2)_nNR_4R_{14}$, or $(CH_2)_nN(R_2')(R_2'')$.

In yet another embodiment, X is $(CH_2)_nNR_4R_{14}$.

In yet another embodiment, X is $(CH_2)_nN(R_2')(R_2'')$.

In one embodiment of the present invention X is R_2, OR_2', $(CH_2)_nNR_4R_{14}$, or $(CH_2)_nN(R_2')(R_2'')$.

Suitably, when X is $(CH_2)_nNR_4R_{14}$, and R_4 and R_{14} are C_{1-10} alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or heteroaryl C_{1-4} alkyl, the C_{1-4} alkyl is suitably substituted one or more times, independently at each occurrence with $NR_{4'}R_{14'}$; halogen, hydroxy, alkoxy, $C(O)NR_{4'}R_{14'}$; or $NR_{4'}C(O)C_{1-10}$alkyl. Preferably, the C_{1-4} alkyl is substituted with $NR_{4'}R_{14'}$.

In one embodiment at least one of R_4 and R_{14} may be hydrogen when R_4 and R_{14} are not cyclized. In another embodiment neither R_4 nor R_{14} is hydrogen.

In one embodiment when X is $(CH_2)_nNR_4R_{14}$, one of R_4 and R_{14} are hydrogen, and the other is an optionally substituted heteroaryl C_{1-4} alkyl. Suitably, the optionally substituted heteroaryl alkyl is an imidazolyl alkyl, such as a 1*H*-imidazol-2-yl-methyl group.

In another embodiment when X is $(CH_2)_nNR_4R_{14}$ and one of R_4 and R_{14} is a heteroaryl C_{1-4} alkyl moiety, the heteroaryl ring is selected from an optionally substituted thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, triazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl. Suitably, the heteroaryl C_{1-4} alkyl is selected from an optionally substituted pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, imidazolyl, benzoxazolyl, benzimidazolyl, and benzothiazolyl.

In another embodiment when X is $(CH_2)_nNR_4R_{14}$ and one of R_4 and R_{14} is a heterocyclic C_{1-4} alkyl moiety, then the heterocyclic ring is selected from an optionally substituted tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholino. Suitably, the heterocyclic C_{1-4} alkyl moiety is selected an optionally substituted from pyrrolinyl, pyrrolidinyl, piperidinyl, piperazinyl, and morpholino.

In another embodiment when X is $(CH_2)_nNR_4R_{14}$ and R_4 and R_{14} together with the nitrogen cyclize to form an optionally substituted ring, such as described above, such rings include, but are not limited to pyrrolidine, piperidine, piperazine, diazepine, and morpholine.

In one embodiment when X is $(CH_2)_nNR_4R_{14}$, the R_4 and R_{14} substituents cyclize to form a heterocyclic 5 or 6 membered ring, which ring is optionally substituted as defined herein. When the R_4 and R_{14} substituents cyclize to form a 4 to 7 membered ring, the optional substitutents are suitably selected from an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, optionally substituted heterocyclic, $(CR_{10}R_{20})_nN(R_{10'})C(Z)OR_7$, $NR_{4'}R_{14'}$, or a C_{1-10} alkyl substituted one or more times by an optionally substituted aryl. Such substitutents more specifically include phenyl, pyrrolidinyl, morpholino, piperazinyl,

4-methyl-1-piperazinyl, piperidinyl, 2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, 5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl, diphenylmethyl, methyl, ethyl, propyl, butyl, amino, methylamino, and dimethylamino.

In one embodiment the X substituent is a 1,4'-bipiperin-1-yl ring which may be optionally substituted such as in 4-methyl-1,4'-bipiperin-1-yl; 4-piperidinylamino, 4-amino-1-piperidinyl, 2,2,6,6-tetramethyl-4-piperidinyl)amino, 4-methyl-1-piperazinyl, (4-morpholinyl)-1-piperidinyl, (4-methyl-1-piperazinyl)-1-piperidinyl, 4-ethyl-1-piperazinyl, (2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 5-chloro-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl, 4-(1-pyrrolidinyl)-1-piperidinyl, 4-(diphenylmethyl)-1-piperazinyl, 4-methylhexahydro-1H-1,4-diazepin-1-yl, 4-propyl-1-piperazinyl, or 4-butyl-1-piperazinyl. In a further embodiment, the X substituent is an optionally substituted 1,4'-bipiperin-1'yl ring, a 4-amino-1-piperidinyl, or a 2,2,6,6-tetramethyl-4-piperidinyl)amino.

In another embodiment, when X is $(CH_2)_nN(R_2')(R_2'')$, and R_2' is an optionally substituted C_{1-10} alkyl moiety, and the alkyl is substituted by $(CR_{10}R_{20})_nNR_eR_e'$, and R_e and R_e' are hydrogen, or an optionally substituted C_{1-10} alkyl. Suitably, the X moiety is 3-(diethylamino)propylamino, 3-(dimethylamino)propyl(methyl)amino, 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-(methylethyl)amino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or a 2-(dimethylamino)ethyl(methyl)amino.

In another embodiment when X is $(CH_2)_nN(R_2')(R_2'')$, and R_2' moiety is an optionally substituted heteroarylC_{1-10} alkyl, the heteroaryl moiety is suitably an optionally substituted imidazole.

In one embodiment of the invention at least one of R_4 and R_{14} may be hydrogen when R_4 and R_{14} are not cyclized.

In one embodiment R_3 is a 2,6-difluoro phenyl, R_1' is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2; and R_1 is selected from $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, or $C(Z)O(CR_{10}R_{20})_vR_b$, or $N(R_{10}')C(Z)(CR_{10}R_{20})_vR_b$. Further to this embodiment, R_1 is selected from $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$. In another embodiment, the R_b moiety is selected from thiazolyl, C_{1-10} alkyl or an optionally substituted aryl. In another embodiment the R_b moiety is propyl or 4-fluorophenyl.

In another embodiment, X is suitably selected from (1*H*-imidazol-2-ylmethyl)amino or 4-methyl-1,4'-bipiperidin-1'-yl, 2,2,6,6-tetramethyl-4-

piperidinyl)amino, 4-amino-1-piperidinyl, 3-(diethylamino)propylamino, 3-(dimethylamino)propyl(methyl)amino , 3-(dimethylamino)propyl(methyl)amino, 2-(dimethylamino)ethylamino, 1-methylethyl)amino-propylamino, (1,1-dimethylethyl)aminopropylamino, (1-methylethyl)aminoethylamino, 2-(methylamino)ethylamino, 2-aminoethyl(methyl)amino, or 2-(dimethylamino)ethyl(methyl)amino.

In one embodiment, R_3 is a 2,6-difluoro phenyl, R_1' is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2; and R_1 is selected from $C(Z)N(R10')(CR_{10}R_{20})_vR_b$, R_b moiety is C_{1-10} alkyl or an optionally substituted aryl, preferably propyl or 4-fluorophenyl, X is $(CH_2)_nN(R_2')(R_2'')$, and n is 0. In another embodiment, X is $(CH_2)_nN(R_2')(R_2'')$, R_2'' is hydrogen, n is 0, and R_2' is an alkyl substituted by $(CR_{10}R_{20})_nNR_eR_e'$. In a further embodiment, R_e and R_e' are independently selected from an optionally substituted C_{1-4} alkyl, such as methyl, ethyl, isopropyl, n-butyl, or t-butyl, preferably ethyl.

Another embodiment of the invention is the genus of compounds of formula (Ic), a subgenus of compounds of Formula (I) and (Ia) wherein R_1 is $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, and R_b is an optionally substituted heteroaryl, an optionally substituted heteroaryl C_{1-10} alkyl, an optionally substituted heterocyclic or an optionally substituted heterocyclic C_{1-10} alkyl. The remaining groups are the same as enumerated above for Formula (I) and (Ia).

In another embodiment for compounds of Formula (Ic), R_1 is $C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$, and R_b is an optionally substituted heteroaryl, or an optionally substituted heteroaryl C_{1-10} alkyl.

Suitably, the heteroaryl, heteroarylalkyl, heterocyclic and heterocyclicalkyl moieties are as defined above for Formula (I) and (Ia). A preferred heteroaryl ring is an optionally substituted thiazolyl ring, pyridyl, or thiophene ring.

In one embodiment of this invention, for compounds of Formula (I), (Ia), and (Ic), as well as the remaining formulas herein, R_1' is independently selected hydrogen, halogen, C_{1-4} alkyl, or halo-substituted-C_{1-4} alkyl. In another embodiment, R_1' is independently selected from hydrogen, fluorine, chlorine, methyl, or CF_3. In one embodiment when R_1' is substituted on the phenyl ring in the ortho position, and a second R_1' moiety is also substituted on the ring, then preferably the second substitution is not in the other ortho position.

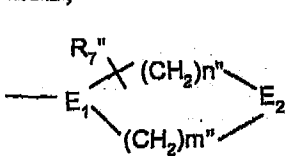
In one embodiment of the invention, g is 1 or 2.

Suitably, in one embodiment when R_3 is an aryl moiety, it is a phenyl ring, and the phenyl ring is optionally substituted, independently at each occurrence, one or more times, suitably 1 to 4 times by halogen, C_{1-4} alkyl, or halo-substituted-C_{1-4} alkyl. The phenyl ring may suitably be substituted in the 2, 4, or 6-position, or di-substituted in the 2,4- position, such as 2-fluoro, 4-fluoro, 2,4-difluoro, 2,6-difluoro, 6-difluoro, or 2-methyl-4-fluoro; or tri-substituted in the 2,4,6-position, such as 2,4,6-trifluoro. Preferably, R_3 is a 2,6-difluoro phenyl.

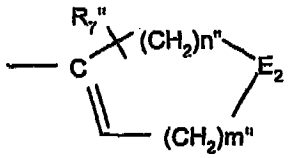
In one embodiment, R_3 is a 2,6-difluoro phenyl, R_1' is independently selected at each occurrence from hydrogen, fluorine, or methyl; g is 1 or 2.

In another embodiment of the present invention, for compound of Formula(s) (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), (VIII) and (VIIIa), (A), (A1), (B) and (B1) the X term may also be the B-Non-Ar-cyc moiety as disclosed in US 6,809,199 whose disclosure is incorporated by reference herein.

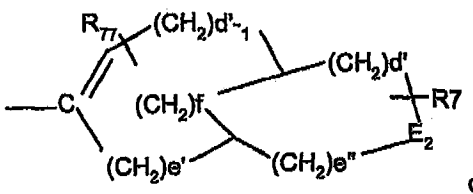
As represented by the disclosure in US 6,809,199, Non-Ar-Cyc is suitably selected from;



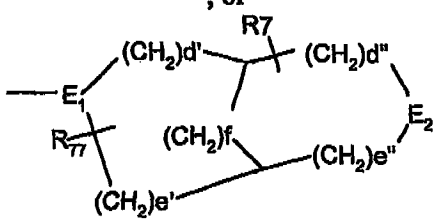
, or



, or



or



wherein

d is an integer having a value of 1, 2, 3, or 4;

d' is 0, or an integer having a value of 1, 2, or 3;

d" is 0, or an integer having a value of 1, 2, or 3;

e is 0, or is an integer having a value of 1, 2, 3, or 4;

e' is 0, or an integer having a value of 1, 2, or 3;

e" is 0, or an integer having a value of 1, 2, or 3;

f is 0, or is an integer having a value of 1, 2, or 3;

d + e is 2, 3, 4, 5, or 6;

d' + e" = d

e' + e" = m

Suitably, $R_{7'}$, R_{77} and $R_{77''}$ are each independentlyselcted from hydrogen, C_{1-6} alkyl-group, C_{2-6} alkenyl-group, C_{4-6} cycloalkyl-C_{0-6} alkyl-group, N(C_{0-4} alkyl)(C_{0-4} alkyl)-C1-4 alkyl-N(C_{0-4} alkyl)-group, -N(C_{0-4} alkyl)(C_{0-4} alkyl) group, C_{1-3} alkyl-CO—C_{0-4} alkyl-group, C_{0-6} alkyl-O--C(O)—C_{0-4} alkyl-group, C_{0-6} alkyl-C(O)-O—C_{0-4}alkyl-group, N(C_{0-4} alkyl)(C_{0-4} alkyl)-(C_{0-4} alkyl)C(O)(C_{0-4} alkyl)-group, phenyl-C_{0-4} alkyl-group, pyridyl-C_{0-4} alkyl-group, pyrimidinyl-C_{0-4} alkyl-group, pyrazinyl-C_{0-4} alkyl-group, thiophenyl-C_{0-4} alkyl-group, pyrazolyl-C_{0-4} alkyl-group, imidazolyl-C_{0-4} alkyl-group, triazolyl-C_{0-4} alkyl-group, azetidinyl-C_{0-4} alkyl-group, pyrrolidinyl-C_{0-4} alkyl-group, isoquinolinyl-C_{0-4}alkyl-group, indanyl-C_{0-4} alkyl-group, benzothiazolyl-C_{0-4} alkyl-group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being -OH, -N(C_{0-4} alkyl)(C_{0-4}alkyl), C_{1-4}alkyl , C_{1-6} alkoxyl, C_{1-6} alkyl-CO—C_{0-4} alkyl-, pyrrolidinyl-C_{0-4} alkyl-, or halogen; or $R_{7'}$ together with a bond from an absent ring hydrogen is =O.

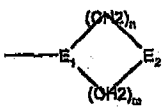
Suitably, B is -C_{1-6}alkyl-, -C_{0-3} alkyl-O-C_{0-3}alkyl-, -C_{0-3} alkyl-NH-C_{0-3}alkyl-, -C_{0-3}alkyl-NH-C_{3-7}cycloalkyl-, -C_{0-3}alkyl-N(C_{0-3}alkyl)-C(O)-C_{0-3} alkyl-, -C_{0-3} alkyl-NH--SO_2-C_{0-3} alkyl-, -C_{0-3} alkyl-, -C_{0-3}alkyl-S-C_{0-3} alkyl-, -C_{0-3} alkyl-SO_2 -C_{0-3}alkyl-, -C_{0-3}alkyl-PH-C_{0-3} alkyl-, C_{0-3} alkyl -C(O)-C_{0-3} alkyl, or a direct bond.

Suitably, E_1 is CH, N, or CR_{66} ; or B and E_1 together form a double bond, i.e., –CH=C.

Suitably, E_2 is CH_2, CHR_{77}, C(OH)R_{77} NH, NR_{77}, O, S, -S(O)-, or -$S(O)_2$ -.

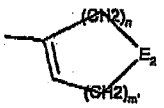
Suitably, R_{66} is independently selected from at each occurrence from halogen, C_{0-4} alkyl, -C(O)-O (C_{0-4} alkyl), or –C(O)-N(C_{0-4} alkyl)-(C_{0-4} alkyl).

In an alternative embodiment of this invention, Non-Ar-Cyc is:



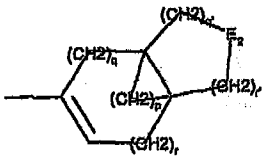
n = 1 to 4
m = 0 to 4
n+m = 2 to 6

E1 = CH, CR6, N or B-E1 can equal double bond (C=C) ; or



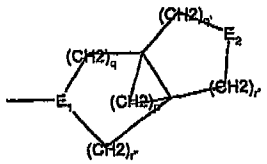
n = 1 to 4
m' = 0 to 3
n+m' = 1 to 5

; or



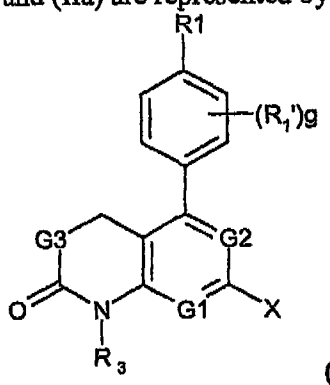
p = 0 to 3
q = 0 to 4
q' = 0 to 4
r = 0 to 4
r' = 0 to 4
q+q'+r+r' = 2 to 6

; or

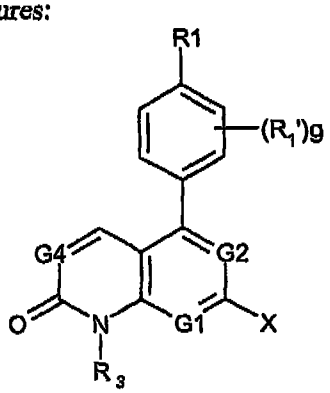


In another embodiment of the present invention, for compound of Formula(s) (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), (VIII) and (VIIIa), (A), (A1), (B) and (B1) the X term may also be the X moiety as disclosed in WO 2004/073628, published September 2004, Boehm et al., whose disclosure is incorporated by reference herein.

In another embodiment of the present invention, compounds of Formula (II) and (IIa) are represented by the structures:



(II)



(IIa)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or

heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, OR_2', $S(O)_mR_2'$, $(CH_2)_n'N(R_{10}')S(O)_mR_2'$, $(CH_2)_n'N(R_{10}')C(O)R_2'$, $(CH_2)_n'NR_4R_{14}$, $(CH_2)_n'N(R_2')(R_2'')$, or $N(R_{10}')$-R_h-NH-C(=N-CN)NRqRq';

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10}')CH_2-CH_2-$, $-CH_2-N(R_{10}')C(O)CH_2-$, $-CH_2-CH(OR_{10}')-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and R_q' are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and R_q' together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_q'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q'C(A_1)(A_2)(A_3)$;

R_2' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_2'' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein R_2'' is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of

these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;
n' is 0 or an integer having a value of 1 to 10;
m is 0 or an integer having a value of 1 or 2;
q is 0 or an integer having a value of 1 to 10;
q' is 0, or an integer having a value of 1 to 6;
t is an integer having a value of 2 to 6;
v is 0 or an integer having a value of 1 or 2;
v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Representative examples of compounds of Formula (II) and (IIa) are:
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-1,3-thiazol-2-ylbenzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(1-methylethyl)benzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-propylbenzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-phenylbenzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)benzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*-dimethylbenzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-methylbenzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzamide
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-(1-methylethyl)benzamide

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-propylbenzamide

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-phenylbenzamide

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-3-methylbenzamide

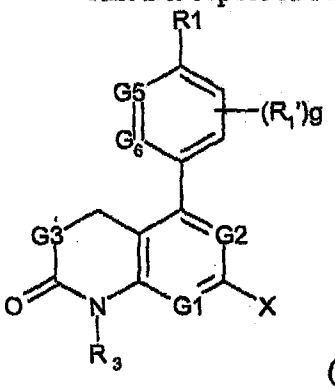
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*,3-trimethylbenzamide

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,3-dimethylbenzamide

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzamide; or

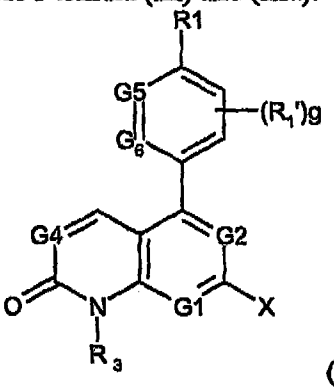
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds Formula (III) and (IIIa):



(III)

or



(IIIa)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_5 and G_6 are independently selected from nitrogen or CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

R_1' is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)$N(R_{10'})CH_2$-CH_2-, -CH_2-$N(R_{10'})C(O)CH_2$-, -CH_2-$CH(OR_{10'})$-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR4'R14', excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl,

arylC1-4 alkyl, heteroaryl, heteroarylC1-4 alkyl, heterocyclyl, or a heterocyclylC1-4 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C1-4 alkyl, C3-6 cycloalkyl, C3-6 cycloalkylC1-4alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

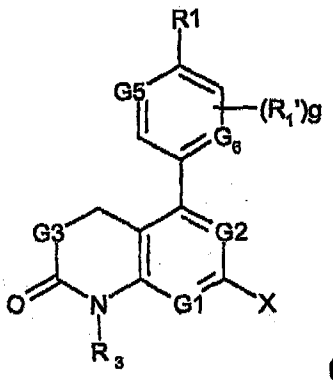
v' is 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

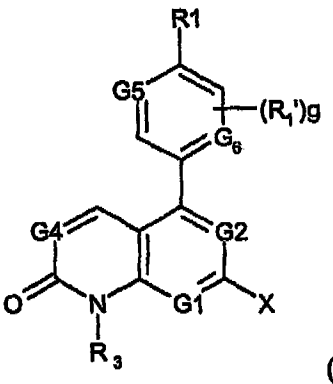
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

It should be recognized that the difference between compounds of Formula (I) and (Ia), and Formula (II) and (IIa) and those of Formulas (III) and (IIIa) through Formula (V) and (Va) lie not only in the in the ring substitution of the R1 group, but that the ring position of the nitrogen in the pyridyl ring. All of the remaining variables have the same meaning for Formulas (III) and (IIIa) through Formula (V) and (Va) as those described herein for Formula (I) and (Ia), etc.

Another aspect of the invention are compounds of Formula (IV) and (IVa):



(IV) or



(IVa)

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_5 and G_6 are independently selected from nitrogen or CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)NRqRq';

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally

substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_q{}'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q{}'C(A_1)(A_2)(A_3)$;

$R_2{}'$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_2{}''$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_2{}''$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_4{}'$ and $R_{14}{}'$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_4{}'$ and $R_{14}{}'$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_9{}'$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_4'R_{14}'$, excluding the moieties SR_5 being $SNR_4'R_{14}'$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

R_9' is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{10}' is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

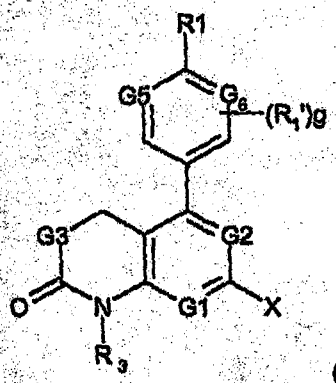
v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;

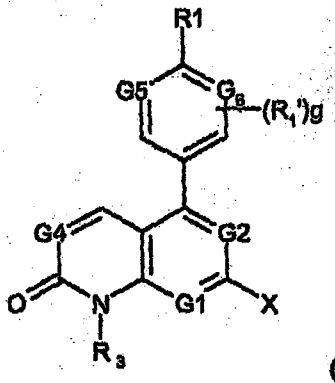
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds Formula (V) and (Va):



(V) or



(Va)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_5 and G_6 are nitrogen and CH, provided that only one of G5 or G6 is nitrogen and the other is CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

R_1' is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)NRqRq';

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)$N(R_{10'})CH_2$-CH_2-, -CH_2-$N(R_{10'})C(O)CH_2$-, -CH_2-CH($OR_{10'}$)-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_q{}'X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q{}'C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members,

which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

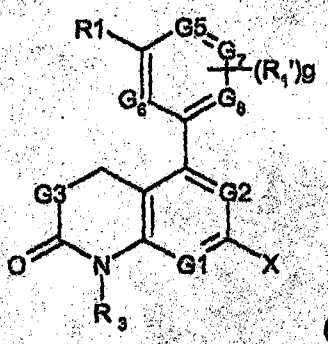
q' is 0, or an integer having a value of 1 to 6;

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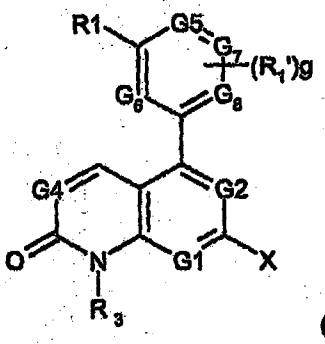
t is an integer having a value of 2 to 6;
v is 0 or an integer having a value of 1 or 2;
v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

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Another aspect of the invention are compounds formula (VI) and (VIa):



(VI) or



(VIa)

wherein
G_1, and G_2 are independently nitrogen;
G_3 is NH;
G_4 is nitrogen;
one of G_5, G_6, G_7 and G_8 is nitrogen and the others are CH;
R_1 is $C(Z)N(R10')(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R10')(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;
R_1' is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;
R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;
X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;
X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl,

heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

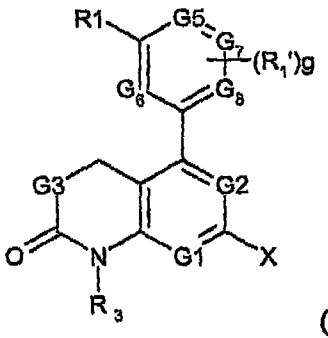
R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$;

g is 0 or an integer having a value of 1, 2, 3, or 4;

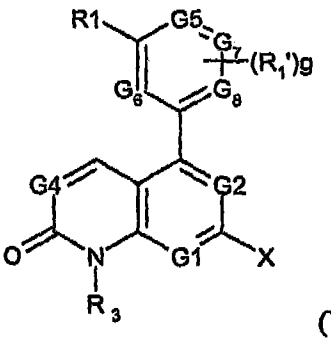
n' is 0 or an integer having a value of 1 to 10;
m is 0 or an integer having a value of 1 or 2;
q is 0 or an integer having a value of 1 to 10;
q' is 0, or an integer having a value of 1 to 6;
t is an integer having a value of 2 to 6;
v is 0 or an integer having a value of 1 or 2;
v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

It should be recognized that the difference between compounds of Formula (I) and (Ia), and Formula (II) and (IIa) and those of Formulas (VII) through Formula (VIi) lie not only in the in the ring substitution of the R1 group, but that the ring position of the two nitrogen's in the pyrimidine ring. All of the remaining variables have the same meaning for Formulas (VI) through Formula (VIi) as those described herein for Formula (I) and (Ia), etc.

Another aspect of the invention are compounds of Formula (VIb) and (VIc):



(VIb) or



(VIc)

wherein
G_1, and G_2 are independently nitrogen;
G_3 is NH;
G_4 is nitrogen;
G_5 and G_6 are nitrogen; and
G_7 and G_8 are CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)NRqRq';

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10}

alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

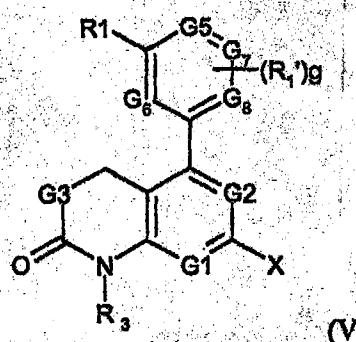
v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;

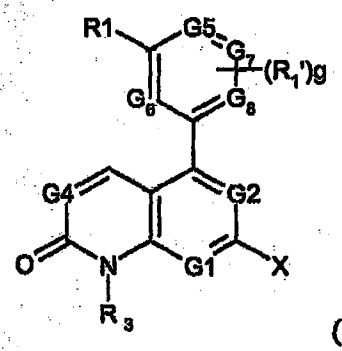
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds Formula (VId) and (VIe):



(VId) or



(VIe)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_6 and G_8 are nitrogen;

G_5 and G_7 are CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl

moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl,

C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

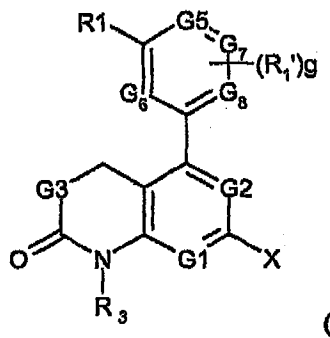
v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;

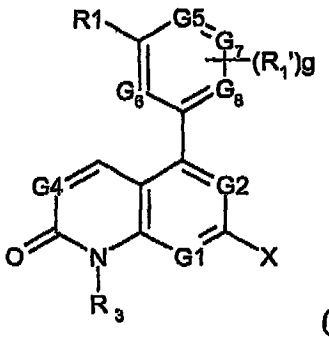
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds Formula (VIf) and (VIg):



(VIf) or



(VIg)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_5 and G_8 are nitrogen;

G_6 and G_7 are CH;

R_1 is $C(Z)N(R_{10}'')(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10}')C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10}')C(Z)N(R_{10}')(CR_{10}R_{20})_vR_b$; or $N(R_{10}')OC(Z)(CR_{10}R_{20})_vR_b$;

R_1' is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10}')S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10}')C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10}')$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10}')CH_2-CH_2-$, $-CH_2-N(R_{10}')C(O)CH_2-$, $-CH_2-CH(OR_{10}')-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together

with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached

form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_4'R_{14}'$, excluding the moieties SR_5 being $SNR_4'R_{14}'$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

R_9' is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{10}' is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

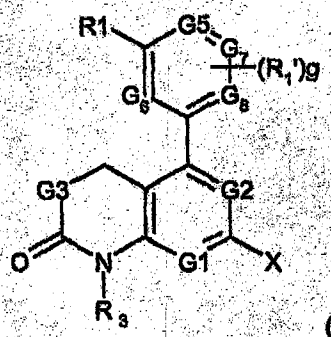
v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;

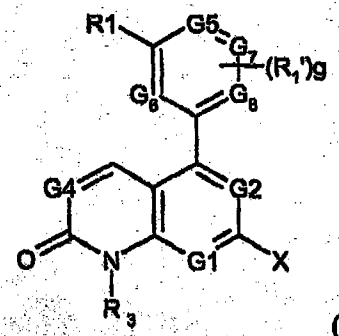
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspect of the invention are compounds of the formula (VIh) and (VIi):



(VIh)



(VIi)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

G_6 and G_7 are nitrogen;

G_5 and G_8 are CH;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, $-CH_2-C(O)-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-C(O)N(R_{10'})CH_2-CH_2-$, $-CH_2-N(R_{10'})C(O)CH_2-$, $-CH_2-CH(OR_{10'})-CH_2$, $-CH_2-C(O)O-CH_2-CH_2-$, or $-CH_2-CH_2-O-C(O)\ CH_2-$;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members,

which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$;

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

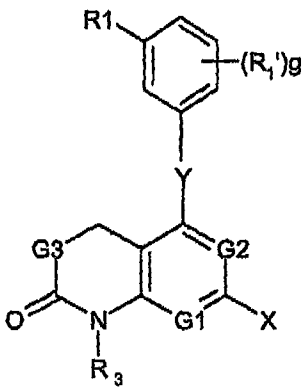
m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

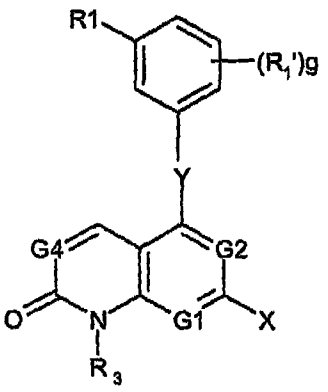
q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;
v is 0 or an integer having a value of 1 or 2;
v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Another aspectof the invention are compounds of Formula (A) and (A1):



(A) or



(A1)

wherein
G_1, and G_2 are independently nitrogen;
G_3 is NH;
G_4 is nitrogen;
Y is $C(R_X)(R_Z)$, C(O), $N(R_Z)$, $N(R_W)C(R_Y)(R_Z)$, oxygen, $OC(R_Y)(R_Z)$, S(O)m, or $S(O)_mC(R_Y)(R_Z)$;
R_X is hydrogen, C 1-2 alkyl, $N(R_V)_2$, hydroxy, thio, C 1-2 alkoxy, or $S(O)_mC_{1-2}$ alkyl;
R_Y is hydrogen or C 1-2 alkyl;
R_Z is hydrogen or C 1-2 alkyl;
R_W is hydrogen or C 1-2 alkyl;
R_V is independently selected from hydrogen or C_{1-2} alkyl;
R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

R_1' is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)$N(R_{10'})CH_2$-CH_2-, -CH_2-$N(R_{10'})C(O)CH_2$-, -CH_2-$CH(OR_{10'})$-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl,

arylC1-4 alkyl, heteroaryl, heteroarylC1-4 alkyl, heterocyclyl, or a heterocyclylC1-4 alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C1-4 alkyl, C3-6 cycloalkyl, C3-6 cycloalkylC1-4alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

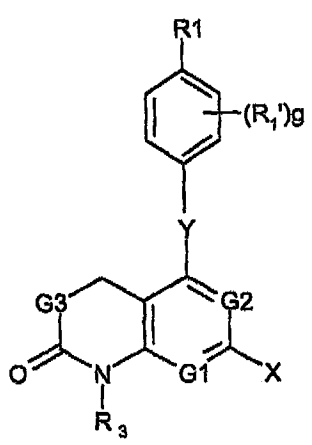
v' is 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur; and

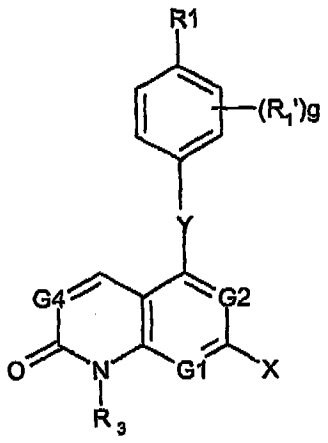
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

The present invention is directed to novel compounds of Formula (A) and Formula (A1), or a pharmaceutically acceptable derivative thereof. As will be readily recognized, the difference between compounds of Formula (A) and Formula (A1), and that of Formula (I) and (Ia) lies in the linker Y. The respective R_1, R_2, and R_3, etc. terms are the same for both groups. For purposes herein, everything applicable to Formula (I) is also applicable to Formula (A) unless otherwise indicated.

Another aspect of the invention are compounds of Formulas (B) and (B1):



(B) or



(B1)

wherein

G_1, and G_2 are independently nitrogen;

G_3 is NH;

G_4 is nitrogen;

Y is $C(R_X)(R_Z)$, $C(O)$, $N(R_Z)$, $N(R_W)C(R_Y)(R_Z)$, oxygen, $OC(R_Y)(R_Z)$, S(O)m, or $S(O)_mC(R_Y)(R_Z)$;

R_X is hydrogen, C 1-2 alkyl, $N(R_V)_2$, hydroxy, thio, C 1-2 alkoxy, or $S(O)_mC_{1-2}$ alkyl;

R_Y is hydrogen or C 1-2 alkyl;

R_Z is hydrogen or C 1-2 alkyl;

R_W is hydrogen or C 1-2 alkyl;

R_V is independently selected at each occurrence from hydrogen or C 1-2 alkyl;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)N(R_{10}')CH_2-CH_2-, -CH_2-N(R_{10}')C(O)CH_2-, -CH_2-CH(OR_{10}')-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and R_q' are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C_{5-7} cycloalkenyl-C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and R_q' together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; *or*

R_2 is the moiety $(CR_{10}R_{20})_q$'$X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_q$'$C(A_1)(A_2)(A_3)$;

R_2' is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_2" is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein R_2" is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl,

heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R4 and R14 together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

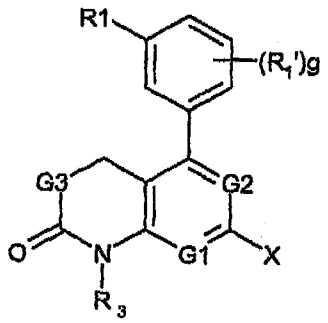
g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;
m is 0 or an integer having a value of 1 or 2;
q is 0 or an integer having a value of 1 to 10;
q' is 0, or an integer having a value of 1 to 6;
t is an integer having a value of 2 to 6;
v is 0 or an integer having a value of 1 or 2;
v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

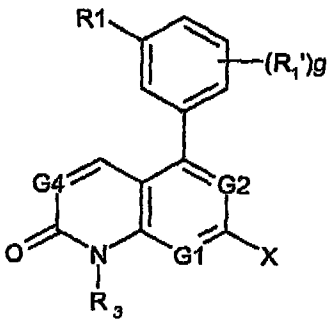
As will be readily recognized, the differences between compounds of Formula (B) and Formula (B1), and that of Formula (II) and (IIa) lie in the linker Y. The respective R_1, R_2, and R_3, etc. terms are the same for both groups. For purposes herein, everything applicable to Formula (II) is also applicable to Formula (B) unless otherwise indicated.

In another aspect of the invention, it is the linker Y may be present in a similar manner in the same position for all of the remaining formulas, Formula's (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), herein. The respective R_1, R_2, and R_3, etc. terms will be the same for all the groups.

Another aspect of the invention are compounds of Formula (VIII) and (VIIIa):



(VIII) or



(VIIIa)

wherein
G_1, G_2 are independently nitrogen or CH, but G_1, and G_2 are not both nitrogen;
G_3 is NH;
G_4 is nitrogen;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)$N(R_{10'})CH_2$-CH_2-, -CH_2-$N(R_{10'})C(O)CH_2$-, -CH_2-$CH(OR_{10'})$-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10}

alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;

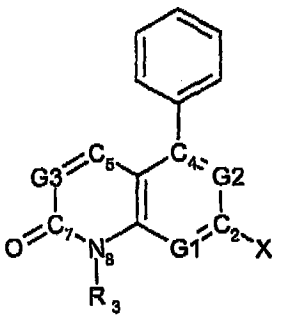
Z is independently selected at each occurrence from oxygen or sulfur; and

a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

In another embodiment of the present invention, for compounds of Formula (VIII) and (VIIIa), and any of the other remaining formulas, the X term may also be the B-Non-Ar-cyc moiety as disclosed above.

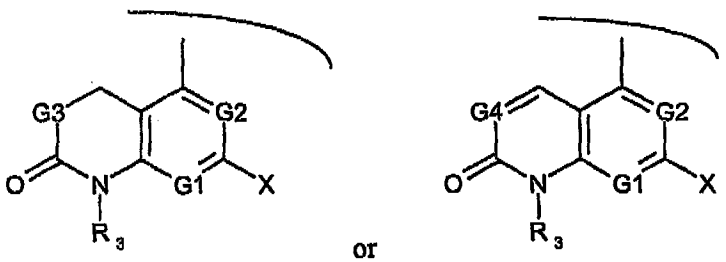
In another embodiment of the present invention, for compound of Formula (VIII) and (VIIIa), and any of the other remaining formulas, the X term may also be the X moiety as disclosed in WO 2004/073628, published September 2004, Boehm et al., whose disclosure is incorporated by reference herein.

For purposes herein the template containing the G_1 and G_2 moieties will have a numbering system that allows for different (R_1 and $R_{1'}$) substituents on the phenyl or pyridyl or pyrimidine ring at the C_4 position; the X term at the C_2 position, and at the R_3 substituent in the N_8 position.



The respective R_1, R_2, R_X, X and R_3, etc., terms are the same for both groups within the formulas themselves, for instance, in Formula (VIII) and (VIIIa). For purposes herein, everything applicable to Formula (VIII) is also applicable to Formula (VIIIa) unless otherwise indicated.

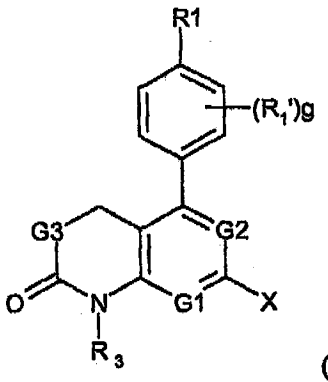
It is recognized that for compounds of Formula (I) and (Ia), etc. and those of Formula (VIII) and (VIIIa) the difference is in the allowance of the G_1 and G_2 moieties to be carbon or nitrogen, independently. For purposes of brevity herein, the remaining compounds of Formulas (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi), may also have the same pharmacophore template of:



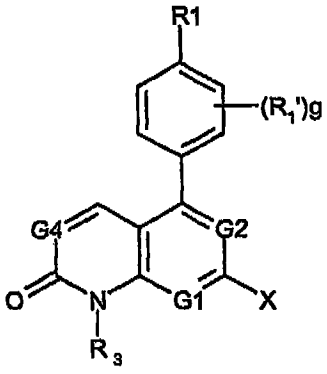
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Illustrative of this would be the C4 substitution from compounds of formula (II) and (IIa) on this pharmacophore template, represented by the structure:



(IX) or



(IXa)

wherein

G_1, and G_2 are independently nitrogen or CH, but G_1, and G_2 are not both nitrogen;

G_3 is NH;

G_4 is nitrogen;

R_1 is $C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$, $C(Z)O(CR_{10}R_{20})_vR_b$, $N(R_{10'})C(Z)(CR_{10}R_{20})_vR_b$; $N(R_{10'})C(Z)N(R_{10'})(CR_{10}R_{20})_vR_b$; or $N(R_{10'})OC(Z)(CR_{10}R_{20})_vR_b$;

$R_{1'}$ is independently selected at each occurence from halogen, C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, cyano, nitro, $(CR_{10}R_{20})_{v'}NR_dR_{d'}$, $(CR_{10}R_{20})_{v'}C(O)R_{12}$, SR_5, $S(O)R_5$, $S(O)_2R_5$, or $(CR_{10}R_{20})_{v'}OR_{13}$;

R_b is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-10} alkyl, aryl, arylC_{1-10}alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

X is R_2, $OR_{2'}$, $S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})S(O)_mR_{2'}$, $(CH_2)_{n'}N(R_{10'})C(O)R_{2'}$, $(CH_2)_{n'}NR_4R_{14}$, $(CH_2)_{n'}N(R_{2'})(R_{2''})$, or $N(R_{10'})$-R_h-NH-C(=N-CN)$NR_qR_{q'}$;

X_1 is $N(R_{11})$, O, $S(O)_m$, or $CR_{10}R_{20}$;

R_h is selected from an optionally substituted C_{1-10} alkyl, -CH_2-C(O)-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-C(O)$N(R_{10'})CH_2$-CH_2-, -CH_2-$N(R_{10'})C(O)CH_2$-, -CH_2-$CH(OR_{10'})$-CH_2, -CH_2-C(O)O-CH_2-CH_2-, or -CH_2-CH_2-O-C(O) CH_2-;

R_q and $R_{q'}$ are independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-10}alkyl, C_{5-7} cycloalkenyl, C $_{5-7}$ cycloalkenyl-C $_{1-10}$alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10}

alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, wherein all of the moieties, excluding hydrogen, are optionally substituted, or R_q and $R_{q'}$ together with the nitrogen to which they are attached form a 5 to 7 membered optionally substituted ring, which ring may contain an additional heteroatom selected from oxygen, nitrogen or sulfur;

R_2 is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or

R_2 is the moiety $(CR_{10}R_{20})_{q'}X_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$, or $(CR_{10}R_{20})_{q'}C(A_1)(A_2)(A_3)$;

$R_{2'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

$R_{2''}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylalkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic, or a heterocyclylC_{1-10} alkyl moiety, and wherein these moieties, excluding hydrogen, may be optionally substituted; or

wherein $R_{2''}$ is the moiety $(CR_{10}R_{20})_tX_1(CR_{10}R_{20})_qC(A_1)(A_2)(A_3)$;

A_1 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_2 is an optionally substituted C_{1-10} alkyl, heterocyclic, heterocyclic C_{1-10} alkyl, heteroaryl, heteroaryl C_{1-10} alkyl, aryl, or aryl C_{1-10} alkyl;

A_3 is hydrogen or is an optionally substituted C_{1-10} alkyl;

R_3 is C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroarylC_{1-10} alkyl, or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted;

R_4 and R_{14} are each independently selected at each occurrence from hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkylC_{1-4}alkyl, aryl, aryl-C_{1-4} alkyl, heterocyclic, heterocyclic C_{1-4} alkyl, heteroaryl or a heteroaryl C_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or the R_4 and R_{14} together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 4 to 7 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or nitrogen;

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$R_{4'}$ and $R_{14'}$ are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or $R_{4'}$ and $R_{14'}$ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from $NR_{9'}$;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_{4'}R_{14'}$, excluding the moieties SR_5 being $SNR_{4'}R_{14'}$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

$R_{9'}$ is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

$R_{10'}$ is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{11} is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_d and $R_{d'}$ are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and $R_{d'}$ together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or $NR_{9'}$;

g is 0 or an integer having a value of 1, 2, 3, or 4;

n' is 0 or an integer having a value of 1 to 10;

m is 0 or an integer having a value of 1 or 2;

q is 0 or an integer having a value of 1 to 10;

q' is 0, or an integer having a value of 1 to 6;

t is an integer having a value of 2 to 6;

v is 0 or an integer having a value of 1 or 2;

v' is 0 or an integer having a value of 1 or 2;
Z is independently selected at each occurrence from oxygen or sulfur; and
a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

Therefore, compounds having the C4 position substitution from Formula (III) and (IIIa) with the G1/G2 pharmacophore template of carbon or nitrogen, would be considered compounds of Formula (X) and (Xa), etc.

Suitably *synthesis to make* compounds of Formula (VIII), (IX), (X), etc., are known to the skilled artisan in this field. Similar processes are provided for in WO 2004/073628, published September 2004, Boehm et al., and in US 6,809,199 whose disclosures are incorporated herein by reference. It is also recognized that in order to have the variety of different R_1, R_2, X, and R_3 groups, etc. some optional substituents may need to be suitably protected to achieve compatibility with the reactions as outlined therein. Subsequent deprotection in those cases would then afford compounds of the nature generally disclosed.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove. It is also to be understood that the present invention encompasses compounds of formula (I) in which a particular group or parameter, for example R_5, R_6, R_9, R_{10}, R_{11}, R_{12}, R_{13}, p, n, or q, etc. may occur more than once. In such compounds it will be appreciated that each group or parameter is independently selected from the values listed. When any variable occurs more than one time in a Formula (as described herein), its definition on each occurrence is independent of its definition at every other occurrence.

Particular *compounds according to* the invention include those mentioned in the examples and their pharmaceutically derivatives.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical and veterinary usage. Salts and solvates of compounds of the invention which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of the invention and their pharmaceutically acceptable salts and solvates.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate or prodrug e.g. ester, of a compound of the

invention, which upon administration to the recipient is capable of providing (directly or indirectly) a compound of the invention, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol. 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. In one embodiment pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. In another embodiment pharmaceutically acceptable derivatives are salts, solvates and esters. In yet another embodiment of the invention pharmaceutically acceptable derivatives are salts and esters, in particular salts.

The compounds of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutical acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Salts of the compounds of the present invention may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I). Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Suitable addition salts are formed from acids which form non-toxic salts and examples are acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, ethanesulphonate, formate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydrogen phosphate, hydroiodide, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, oxaloacetate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, piruvate, polygalacturonate, saccharate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate and valerate.

Pharmaceutically acceptable base salts include ammonium salts such as a trimethylammonium salt, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases, including salts of primary, secondary and tertiary amines, such as

isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexyl amine and N-methyl-D-glucamine.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula (I), or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water. A complex with water is known as a "hydrate". Solvates of the compound of the invention are within the scope of the invention.

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series; Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

Prodrugs are any covalently bonded carriers that release a compound of formula (I) *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy or amine groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol and amine functional groups of the compounds of formula (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; halosubstituted C_{1-10} alkoxy; S(O)m alkyl, such as methyl thio, methylsulfinyl or methyl sulfonyl; a ketone (-C(O)), or an aldehyde (-C(O)$R_{6'}$), such as C(O)C_{1-10} alkyl or C(O)aryl, wherein $R_{6'}$ is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl (and wherein the $R_{6'}$ moieties, excluding hydrogen, may themselves be optionally substituted 1 or 2 times, independently by halogen; hydroxy; hydroxy substituted alkyl; C_{1-4} alkoxy; $S(O)_mC_{1-4}$ alkyl; amino, mono & di-substituted C_{1-4} alkyl amino; C_{1-4} alkyl, or CF_3); C(O)$OR_{6'}$; $NR_{4'}R_{14'}$, wherein $R_{4'}$ and $R_{14'}$ are each independently hydrogen or C_{1-4} alkyl, such as amino or mono or -disubstituted C_{1-4} alkyl or wherein the $R_{4'}R_{14'}$ can cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally contains an additional heteroatom selected from O/N/S; C_{1-10} alkyl, C_{3-7}cycloalkyl, or C_{3-7}cycloalkyl C_{1-10} alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C_{1-10} alkyl, such CF_2CF_2H, or CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl containing moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-4} alkoxy; $S(O)_m$ C_{1-4} alkyl; amino, mono & di-substituted C_{1-4} alkyl amino; C_{1-4} alkyl, or CF_3.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, alkyl sulphonic acid derivatives, such as methanesulphonic, or ethanesulphonic, arylsulphonic acid derivatives , such as p-toluenesulphonic, m-toluenesulphonic, benzenesulphonic, camphor sulphonic, 4-chlorobenzenesulphonic, 4-bromobenzenesulphonic, 4-phenylbenzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), phenylacetic, mandelic, salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, cynao, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic,

4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids.

Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The term "halo" or "halogens" is used herein to mean the halogens, chloro, fluoro, bromo and iodo.

As used herein, the term "C_{1-10}alkyl" or "alkyl" or "alkyl$_{1-10}$" is used herein to mean both straight and branched hydrocarbon chain containing the specified number of carbon atoms, e.g. C_{1-10}alkyl means a straight of branched alkyl chain of at least 1, and at most 10, carbon atoms, unless the chain length is otherwise limited. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, sec-butyl, *tert*-butyl or t-butyl and hexyl and the like.

As used herein, the term "alkenyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms and containing at least one double bond. For example, C_{2-6}alkenyl means a straight or branched alkenyl containing at least 2, and at most 6, carbon atoms and containing at least one double bond. Examples of "alkenyl" as used herein include, but are not limited to ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, 3-methylbut-2-enyl, 3-hexenyl, 1,1-dimethylbut-2-enyl and the like.

As used herein, the term "alkoxy" refers to straight or branched chain alkoxy groups containing the specified number of carbon atoms. For example, C_{1-6}alkoxy means a straight or branched alkoxy containing at least 1, and at most 6, carbon atoms. Examples of "alkoxy" as used herein include, but are not limited to, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy and hexyloxy.

As used herein, the term "cycloalkyl" refers to cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Representative examples of "cycloalkyl" as used herein

include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl and the like.

The term "cycloalkenyl" is used herein to mean cyclic radicals, such as a non-aromatic hydrocarbon ring containing a specified number of carbon atoms preferably of 5 to 7 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aryl" is used herein to mean phenyl, naphthyl, and indene.

The terms "heteroaryl ring", "heteroaryl moiety", and "heteroaryl" are used herein to mean a monocyclic five- to seven- membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples of heteroaryl rings include, but are not limited to, furyl, pyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, oxathiadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, and uracil. The terms "heteroaryl ring", "heteroaryl moiety", and "heteroaryl" shall also used herein to refer to fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Each of the fused rings may contain five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, isoindolyl, indazolyl, indolizinyl, azaindolyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothiophenyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, cinnolinyl, purinyl, and phthalazinyl.

The terms "heterocyclic rings", "heterocyclic moieties", and "heterocyclyl" is used herein to mean a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from nitrogen, oxygen, sulphur or oxidized sulphur moieties, such as S(O)m, and m is 0 or an integer having a value of 1 or 2. The terms "heterocyclic rings", "heterocyclic moieties", and "heterocyclyl" shall also refer to fused rings, saturated or partially unsaturated, and wherein one of the rings may be aromatic, or heteroaromatic. Each of the fused rings may have from four to seven ring atoms. Examples of heterocyclyl groups include, but are not limited to, the saturated or partially saturated versions of the heteroaryl moieties as defined above, such as tetrahydropyrrole, tetrahydropyran, tetrahydrofuran, tetrahydrothiophene (including oxidized versions of the sulfur moiety), azepine, diazepine, aziridinyl, pyrrolinyl, pyrrolidinyl, 2-oxo-1-pyrrolidinyl, 3-oxo-1-pyrrolidinyl, 1,3-benzdioxol-5-yl, imidazolinyl, imidazolidinyl, indolinyl, pyrazolinyl,

pyrazolidinyl, piperidinyl, piperazinyl, morpholino and thiomorpholino (including oxidized versions of the sulfur moiety).

The term "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean a C_{1-4} alkyl (as defined above) attached to an aryl, heteroaryl or heterocyclic moiety (as also defined above) unless otherwise indicated.

The term "sulfinyl" is used herein to mean the oxide S(O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S $(O)_2$ moiety.

The term "aroyl" is used herein to mean C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.

The term "alkanoyl" is used herein to mean $C(O)C_{1-10}$ alkyl wherein the alkyl is as defined above.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove. It is also to be understood that the present invention encompasses compounds of formula (I) in which a particular group or parameter, for example R_5, R_6, R_9, R_{10}, R_{11}, R_{12}, R_{13}, n, m, or t, etc. may occur more than once. In such compounds it will be appreciated that each group or parameter is independently selected from the values listed. When any variable occurs more than one time in a Formula (as described herein), its definition on each occurrence is independent of its definition at every other occurrence.

With regard to stereoisomers, the compounds of the Formulas herein may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compound of the invention and where appropriate, the individual tautomeric forms thereof, together with mixtures thereof.

Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or H.P.L.C. A stereoisomeric mixture of the agent may also be prepared from a corresponding

optically pure intermediate or by resolution, such as H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

Furthermore, some of the crystalline forms of the compounds of the Formulas herein may exist as polymorphs, which are included in the present invention.

Exemplified compounds of the compounds of this invention include the racemates, or optically active forms of the compounds of the working examples herein, and pharmaceutically acceptable salts thereof.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

METHODS OF MANUFACTURE

The compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa), (A), (A1), (B) and (B1) may be obtained by applying the synthetic procedures described herein. The synthesis provided for is applicable to producing compounds of the Formulas herein having a variety of different R_1, R_2, X, and R_3 groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While a particular formula with particular substituent groups is shown herein, the synthesis is applicable to all formulas and all substituent groups herein.

Once the nucleus has been established, further compounds of Formula (I) and (Ia), (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI) and (VIa-VIi) may be prepared by applying standard techniques for functional group inter-conversion, well known in the art. For instance: $C(O)NR_4R_{14}$ from CO_2CH_3 by heating with HNR_4R_{14} in CH_3OH with or without catalytic or stoichiometric metal cyanide or Aluminum trimethyl, e.g. NaCN; $OC(O)R_6$ from OH with e.g., $ClC(O)R_6$ in bases such as triethylamine and pyridine; NR_{10}-$C(S)NR_4R_{14}$ from NHR_{10} with an alkylisothiocyanate, or thiocyanic acid and $ClC(S)NR_4R_{14}$; $NR_{10}C(O)OR_6$ from NHR_{10} with an alkyl or aryl chloroformate; $NR_{10}C(O)NR_4H$ from NHR_{10} by treatment with an isocyanate, e.g. $R_4N{=}C{=}O$; NR_{10}-$C(O)R_6$ from NHR_{10} by treatment with Cl-$C(O)R_6$ in pyridine; $C(=NR_{10})NR_4R_{14}$ from $C(NR_4R_{14})S$ with

$H_3NR_{10}^+OAc^-$ by heating in alcohol; $C(NR_4R_{14})SR_6$ from $C(S)NR_4R_{14}$ with R_6-I in an inert solvent, e.g. acetone; $NR_{10}SO_2R_7$ from NHR_{10} by treatment with $ClSO_2R_7$ by heating in bases such as pyridine; $NR_{10}C(S)R_6$ from $NR_{10}C(O)R_6$ by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; $NR_{10}SO_2CF_3$ from NHR_{10} with triflic anhydride and base wherein R_6, R_{10}, R_4 and R_{14} are as defined in Formula (I) herein.

Precursors of the groups R_1, R_2 and R_3, can be other R_1, R_2 and R_3, etc. groups that may be interconverted by applying standard techniques for functional group interconversion. For example, wherein a moiety is a halo substituted C_{1-10} alkyl can be converted to the corresponding C_{1-10} alkylN_3 derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the corresponding C_{1-10}alkylNH_2 compound, which in turn can be reacted with $R_7S(0)_2X'$ wherein X' is halo (e.g., chloro) to yield the corresponding C_{1-10}alkyl$NHS(0)_2R_7$ compound.

Alternatively wherein the moiety is a halo-substituted C_{1-10}-alkyl it can be reacted with an amine $R_4R_{14}NH$ to yield the corresponding C_{1-10}-alkylNR_4R_{14} compound, or can be reacted with an alkali metal salt of R_7SH to yield the corresponding C_{1-10}alkylSR_7 compound.

As noted above, it may be desirable during the synthesis of the compounds of this invention, to derivatize reactive functional groups in the molecule undergoing reaction so as to avoid unwanted side reactions. Functional groups such as hydroxy, amino, and acid groups are typically protected with suitable groups that can be readily removed when desired. Suitable common protecting groups for use with hydroxyl groups and nitrogen groups are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene et al., John Wiley & Sons, New York, New York, (2nd edition, 1991 or the earlier 1981 version). Suitable examples of hydroxyl protecting groups include ether forming groups such as benzyl, and aryl groups such as *tert*-butoxycarbonyl (Boc), silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, $(CR_{10}R_{20})_n$. Amino protecting groups may include benzyl, aryl such as acetyl and trialkylsilyl groups. Carboxylic acid groups are typically protected by conversion to an ester that can easily be hydrolyzed, for example, trichloethyl, *tert*-butyl, benzyl and the like.

Pharmaceutically acid addition salts of compounds of the various Formulas described herein may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

An illustration of the preparation of compounds of the present invention is shown in the scheme below. For purposes herein, the compounds in the Schemes are shown with an S-methyl, or $S(O)_2$-methyl group which is deemed representative of the S(O)m-Rg group, wherein Rg is a C_{1-10} alkyl as described in the Formulas below.

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Preparation of compounds with Formula (I) can be achieved through compound **6**, which in turn may be constructed from either aldehyde **1** or nitrile **2** as shown in **Scheme 1**. Leaving groups (LG, described as Leaving group 1 (LG1) & LG2) in **1** (or **2**), or elsewhere, can be independently selected from –Cl, -Br, -I, or -OTf and these groups can be installed through the transformation of another functional group (e.g. -OH) by following the methods well known in the art (e.g., treatment of the –OH compound with $POCl_3$).

Method A is for conversion of **1** to **2**. Examples of the methods include, but are not limited to condensation with NH_2OH followed by treatment with thionyl chloride ($SOCl_2$) [e.g., Santilli et al., *J. Heterocycl. Chem.* (1971), 445-53] or oxidation of –CHO group to –COOH followed by formation of a primary amide ($-CONH_2$) and treatment with $POCl_3$. Suitable Method A can also be utilized to furnish the conversion of **4** to **3** – **Scheme I.**

Method B is for selective displacement of suitable aldehyde **1** or nitrile **2** with an amine (R_3-NH_2). This type of displacement may be achieved using triethylamine and the desired amine R_3NH_2 in chloroform at room temperature for 10 minutes. The reaction was very effective for a range of alkyl amines (78-95 % yield). For aryl or heteroaryl amines, elevated temperatures (reflux), longer reaction time (24 hours) and presence of NaH (or Na) may be necessary for reaction completion. Use of the base could be omitted when 3 or more equivalent of the desired amine were used. Other suitable bases include but are not limited to pyridine, diisopropyl ethylamine or pyrrolidine, which may also be used in an appropriate organic solvent, including but not limited to THF, diethyl ether, DCM, DMF, DMSO, toluene or dioxane.

Method C is for the reduction of nitrile **3** to amine **5**. **5** may be considered a primary amine (NH_2), a secondary amine (because of -NH(R3)) or an amine (as it contains basic nitrogen). This method includes, but is not limited to BH_3 in appropriate organic solvent, such as THF, DCM, toluene, DMSO, diethyl ether or dioxane. Other suitable reduction reagents, include but are not limited to $NaBH_4$, LAH or DIBAL. Method C may require elevated temperatures (e.g., heating, refluxing or irradiating with microwave). Another example of the method is hydrogenation (H_2) in the presence of transition metals (e.g., Pd/C, Raney-Ni, $PdCl_2$).

Method D is for the cyclization of **5** to **6**. This method requires the presence of a cyclization reagent (e.g., CDI, $COCl_2$, tri-phosgene, or phenyl chloroformate methyl chloroformate). Presence of a suitable base may help the reaction to go to completion and examples of the base include, but not limited to triethyl amine, diisopropylethylamine or pyrrolidine. Reaction solvent can be DCM, THF, toluene, DMSO, or DMF.

Method E is for the installation of group –X [e.g., **6** to **7**, **10** to **(I)**, **11** to **(I)** or **9** to **12**]. This may or may not require first conversion of sulfide (-SMe) to sulfoxide (-SOMe) or sulfone (-SO_2Me). This conversion can be achieved using *meta*-chloroperoxybenzoic acid (mCPBA) in high yield and purity. Suitable oxidation methods for use herein include use of one or two equivalents of *meta*-chloroperoxybenzoic acid (mCPBA) or Oxone®to afford either the sulfoxides or sulfones. Oxidation of the sulfides to sulfoxides or sulfones can also be effected by OsO_4 and catalytic tertiary amine N-oxide, hydrogen peroxide, hydrogen peroxide/NaWO4, and other peracids, oxygen, ozone, organic peroxides, potassium and zinc permanganate, potassium persulfate, and sodium hypochlorite. The subsequent displacement of sulfone group –SO_2Me (likewise, all displacement reactions mentioned below may be achieved using the sulfide –SMe or sulfoxide -SOMe) requires a suitable nucleophile (e.g., amine, alcohol) containing the unit –X. Displacements with amines were usually done with an excess of amine in N-methylpyrrolidine (Barvian et al., *J. Med. Chem.* (2000), 4606-4616). A wide range of primary amines underwent this reaction with excellent yields. In some cases (in O-displacement or sulfonamide formation) an anion of the nucleophile was prepared with base (usually sodium hydride) in DMF (or DMSO) and then added to the sulfone. Yields for these reactions were usually lower. The sulfone may be displaced by primary and secondary alkylamines without additional base catalysis, preferably in a polar aprotic solvent, such as but not limited to, N-methyl pyrrolidin-2-one (NMP), and at varying temperatures depending upon the nucleophilicity of the amine. For instance displacement of the sulfone with ethanolamine, in NMP, occurred in 30 min. at 65° C, while a more hindered amine such as tris(hydroxymethyl)-aminomethane may require elevated temperatures and extended reaction times (80° C over a 24 hour reaction time). The sulfone can also be displaced by a primary or secondary amine with an additional non-nucleophilic base (e.g. DIPEA) in aprotic solvents like DCM, CH_3CN, NMP, and at varying temperatures depending upon the nucleophilicity of the amine.

The sulfone may also be displaced with a substituted arylamine, or heteroarylamine at elevated temperatures, sometimes requiring formation of the aryl

or heteroarylamine anion with sodium hydride, or other suitable base, in DMSO. In addition, the sulfone may be readily displaced with aluminum salts of aryl or heteroaryl amines as previously described in the patent literature (see for example WO 99/32121, whose disclosure is incorporated by reference herein). Likewise, sulfone may be displaced with aryl or heteroaryl or alkyl thiols or alkyl or aryl or heteroaryl alcohols. Analogs containing sulfones as the X substituents may be displaced with sodium alkoxide in the alcohol, or alternatively reactive alkoxide or phenoxide nucleophiles that may be generated from the alcohol or phenol with a suitable base such as sodium, NaH or sodium bistrimethylsilyl amide in a polar aprotic solvent such as DMSO, or run as a neat reaction. Similarly the sulfone may be displaced with carbon nucleophiles. Suitable carbon nucleophiles include, but not limited to aryl Grignard reagents, alkyl Grignard reagents or related organometallics such as organo lithium, zinc, tin, copper or boron. These reactions may, in some cases, require transition metal catalysis such as with Pd or Ni catalysts.

Method F is for coupling with appropriate aryl groups to convert **7** to compounds of Formula (**I**) (or **6** to **10**). This transformation may be achieved using, but not limited to boronic acids (e.g., **F1A**) under Suzuki cross-coupling conditions, employing a palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0). The coupling conditions include the use of appropriate solvents. These solvents include, but are not limited to dioxane, THF, DMF, DMSO, NMP, acetone, water, or a combination or a mixture thereof. Preferably, the solvent is THF/H_20, or dioxane/H_20. The coupling conditions also include the presence of catalytic amount of catalysts and these catalysts include, but not limited to tetrakis(triphenyl-phosphine)-palladium (0), PdCl2, Pd(OAc)2, (CH3CN)2PdCl2, Pd(dppf)2, or [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II).

The coupling reaction may or may not require the presence of a base. Suitable bases include, but are not limited to $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, KOAc or combination or mixture thereof. Preferably, the base is K_2CO_3 and KOAc.

The coupling reaction may or may not require heating. The heating can be carried out with a regular oil bath or microwave irrediations and the temperature can be varied from room temperature to >100 °C, i.e. reflux temperature of the solvent. The coupling reaction may or may not require a sealed reaction vessal and the internal pressure can be varied from one atmosphere to 100 atmospheres.

Alternatively, the cross-coupling may be performed using aryl or heteroaryl organozinc [e.g., aryl/heteroaryl-ZnBr, aryl/heteroaryl -ZnCl, aryl/heteroaryl-Zn-aryl/heteroaryl], organocopper [e.g., (aryl/heteroaryl)$_2$-CuLi], organotin [e.g., aryl/heteroaryl-Sn(CH_3)$_3$, aryl/heteroaryl -Sn($CH_2CH_2CH_2CH_3$)$_3$], (e.g., **F1C**), or

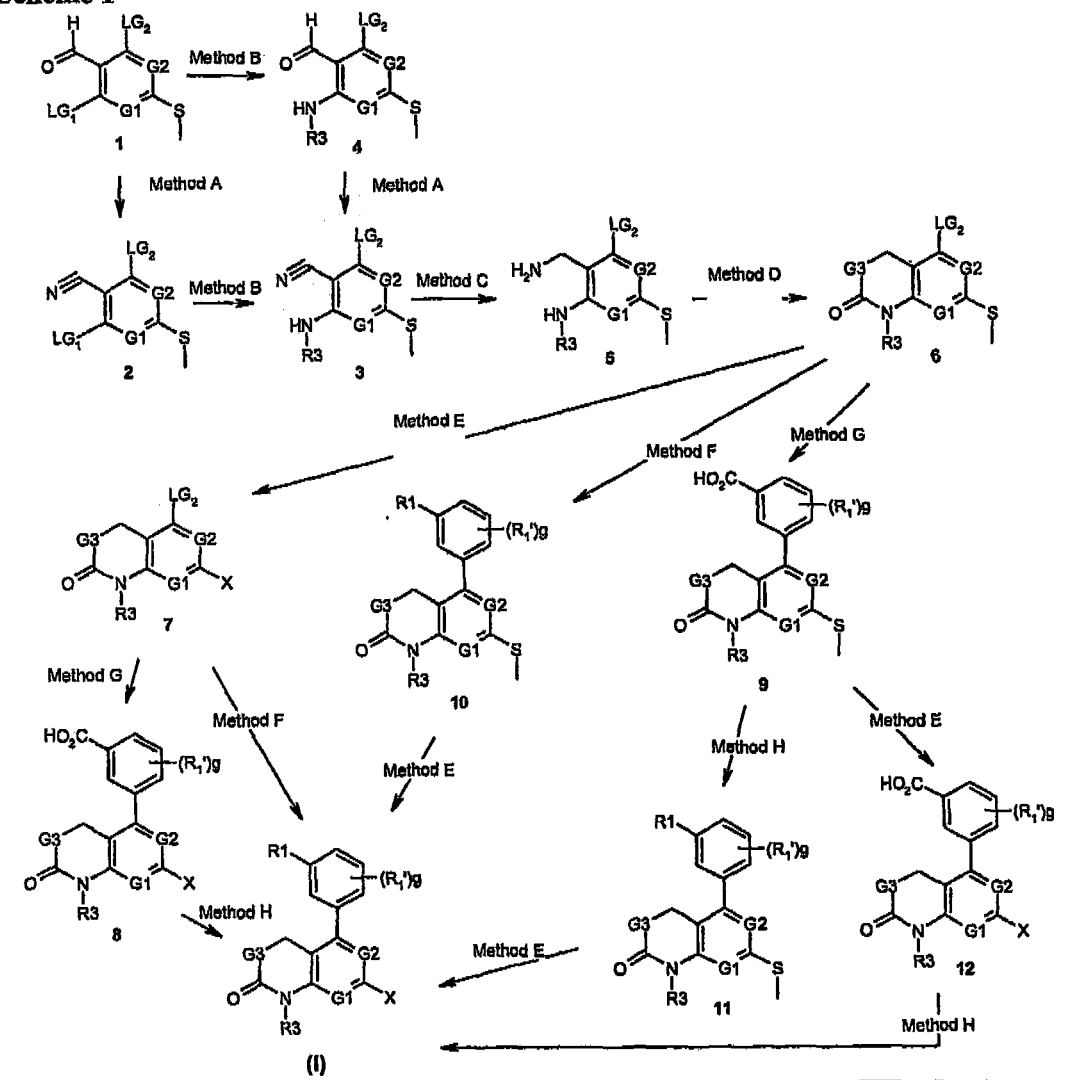
other organometallic reagents (e.g., **F1B**) known in the art [see for example Solberg, J.; Undheim, K. *Acta Chemica Scandinavia* **1989**, 62-68]. These types of coupling reactions require the use of appropriate solvents. Such solvents include, but are not limited to dioxane, THF, methylene chloride, chloroform, benzene, hexane, ethyl ether, *tert*-butyl methyl ether or a combination or a mixture thereof. The coupling reaction may, or may not, require the presence of catalytic amount of a catalyst. Such catalysts include, but are not limited to tetrakis(triphenylphosphine)palladium (0), $PdCl_2$, $Pd(OAc)_2$, $(CH_3CN)_2PdCl_2$, $Pd(dppf)_2$. The reaction temperature can be varied from -78 °C to >100 °C, i.e. reflux temperature of the solvent. Alternatively, this reaction process step may be performed under suitable microwave irradiation conditions, if needed. This reaction may, or may not, require a sealed reaction vessel and the internal pressure can be varied from one atmosphere to 100 atmospheres.

Method G is for coupling of **7** (or **6** or **16**) with an aryl group whose structure has a suitable precursor (e.g., acidic group $-CO_2H$) to the final substituent R_1 in Formula (**I**). This transformation may be achieved using, but not limited to boronic acids (e.g., **G1A**) or protected acids (e.g., **G1C**) under Suzuki coupling conditions, (THF/H_20, and K_2CO_3) employing a palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0). If desired, these Suzuki coupling reactions may be run under microwave conditions. The boronic acid (D1A or D1E) or ester can be synthesized either by the palladium catalyzed coupling of an aryl halide and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi1,3,2-dioxaborolane or the transmetalation of an aryl halide with a Grignard reagent, e.g., isopropylmagnesium bromide followed by a trialkylborate (e.g., triethylborate) in a suitable solvent like THF. Alternatively, the cross-coupling may be performed using aryl or heteroaryl organozinc, organocopper, organotin (e.g., **G1B**), or other organometallic reagents (e.g., **G1D**) known in the art [see for example Solberg, J.; Undheim, K. *Acta Chemica Scandinavia* **1989**, 62-68]. Suitable de-protection is followed if a protected precursor (e.g.,**G3, G4**) is used.

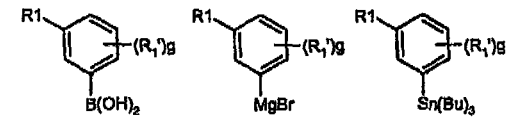
Method H is for the transformation of the suitable precursor (e.g., acidic group –COOH in **8, 9**, or **12**) to the final substituent R_1. This type of transformations can be achieved by utilizing well-established strategies in the art. The transformation may be done in one step (such as coupling with amines $HN(R_{10'})R_b$ under standard coupling conditions e.g. EDC/HOBT/ET_3N in CH_3CN; coupling with alcohol, HOR_b under standard coupling conditions, e.g. DCC, DMAP in DCM to form esters or reduction to alcohol) or in more than one step (e.g., Curtuis rearrangement to form isocyanates followed by urea formation with amines or acid chloride formation

followed by addition of an amine, $HN(R_{10'})R_b$ or an alcohol, HOR_b plus a non-nucleophilic base, e.g. DIPEA in an aprotic solvent like DCM. This conversion may require a deprotection step to install the precursor at first (e.g., hydrolysis of $-CO_2Me$ with LiOH/THF/water to prepare –COOH).

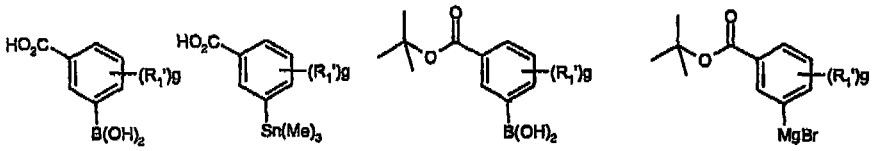
Scheme 1



Examples of Reagents for methods F & G



F1A F1B F1C



G1A G1B G1C G1D

Preparation of compounds with Formula (Ia) can be achieved through compound **14**, which in turn may be constructed from aldehyde **1** as shown in **Scheme 2.** Suitable methods from **Methods A-H** can be utilized to furnish appropriate conversions in **Scheme 2.**

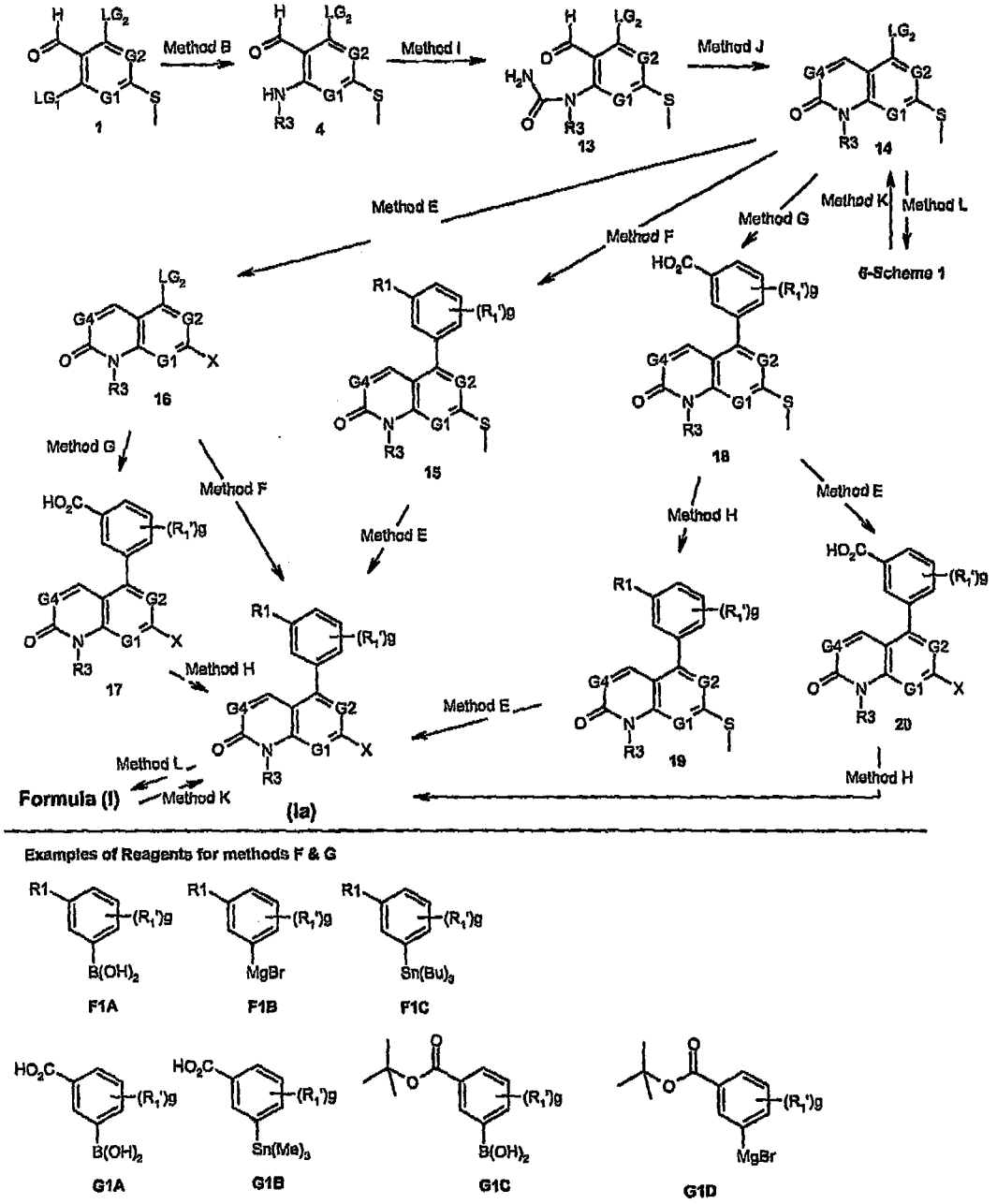
Method I is for urea formation to convert **4** to **13.** This can be achieved by following strategies well-established in the art. Strategies include, but are not limited to reaction with $ClSO_2NCO$ (or Me_3SiNCO) followed by treatment with H_2O, reaction with $COCl_2$ (CDI, or triphosgene) followed by treatment with NH_3 (or NH_4OH), reaction with $ClCO_2Me$ (or $ClCO_2Et$) followed by treatment with NH_3 (or NH_4OH) or reaction with $NH_2CO_2(t\text{-Bu})$.

Method J is for imine formation to convert **13** to **14.** This can be achieved by following various strategies known in the art. Strategies include, but are not limited to treatment with an acid including TFA, HOAc, HCl, H_2SO_4 or a Lewis acid (e.g., AlCl3). This conversion may require elevated temperatures (e.g., heat, solvent reflux, microwave irradiation) in appropriate organic solvents (e.g., THF, CH_2Cl_2, toluene, DMSO, CH_3CN or dioxane).

Method K is an alternative strategy to prepare compounds in **Scheme 2.** This method is for the de-saturation (lose of 2H in the formula) of compounds in **Scheme 1** resulting in the corresponding compounds in **Scheme 2.** This conversion includes, but not limited to **Formula (Ia)-Scheme 2** from Formula **(I)-Scheme 1, 14-Scheme 2** from **6-Scheme 1.** This type of transformations can be achieved by following methods well-known in the art (e.g., treatment with NBS and AIBN in CCl_4 under elevated temperatures, treatment with MnO_2 in chlorobenzene under elevated temperatures).

Method L is for reduction of compounds in **Scheme 2.** This method provides an alternative strategy to synthesize compounds in **Scheme 1** [e.g., **Formula (Ia)-Scheme 2 to Formula (1)-Scheme 1, 14-Scheme 2** to **6-Scheme 1**]. This type of conversion can be achieved by using suitable imine reduction methods published in the art (e.g., treatment with Et_3SiH, $NaBH_4$, H_2-Pd/C).

Scheme 2



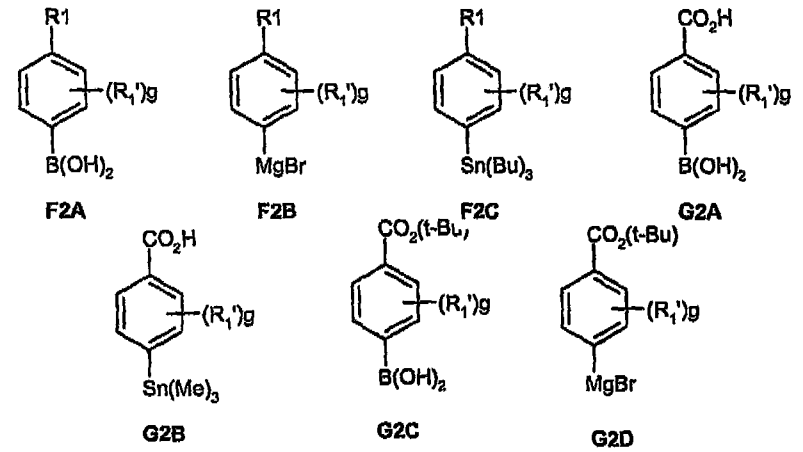
The compounds of Formula (II) and (IIa), (III) and (IIIa), (IV) and (IVa), (V) and (Va), (VI), (VIa-VIi), (VIII) and (VIIIa) may be obtained by applying the synthetic procedures described above in **Scheme 1 &2** except suitable reagents in

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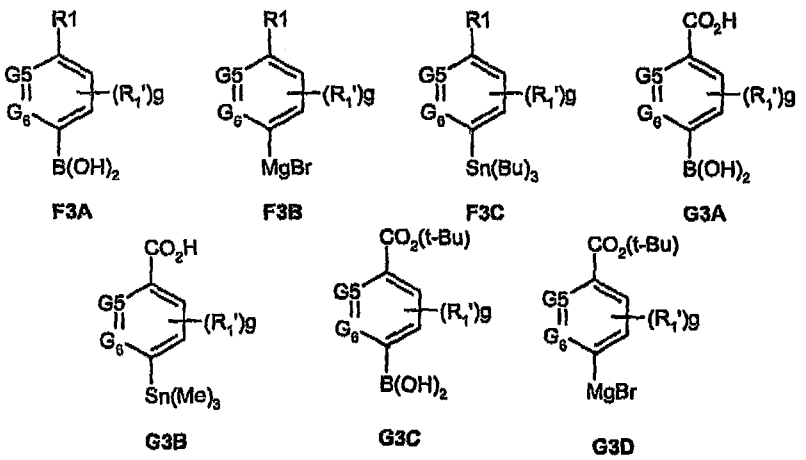
Method F & G should be utilized. Examples of these reagents include, but not limited to those shown in **Scheme 3**. Suitable reagents in **Method F & G** for the preparation of compounds with Formula (VIb-VIi) require the presence of G5-8 in appropriate position.

Scheme 3

Examples of Reagents in Method F & G for the Preparation of Compounds with Formula (II) & (IIa)

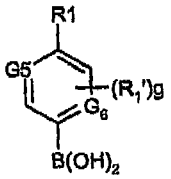


Examples of Reagents in Method F & G for the Preparation of Compounds with Formula (III) & (IIIa)

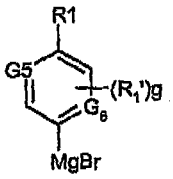


Scheme 3 continued

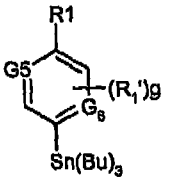
Examples of Reagents in Method F & G for the Preparation of Compounds with Formula (IV) & (IVa)



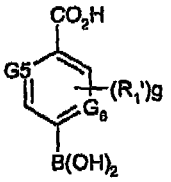
F4A



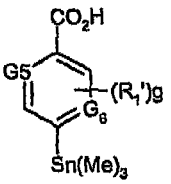
F4B



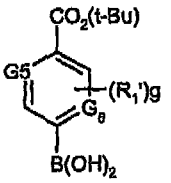
F4C



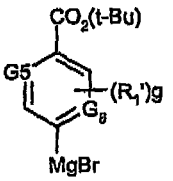
G4A



G4B



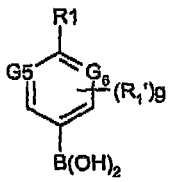
G4C



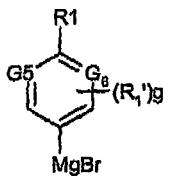
G4D

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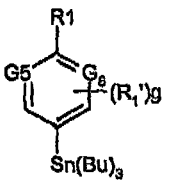
Examples of Reagents in Method F & G for the Preparation of Compounds with Formula (V) & (Va)



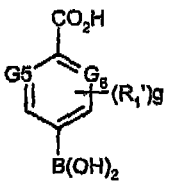
F5A



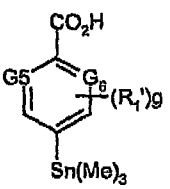
F5B



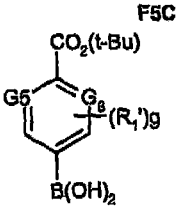
F5C



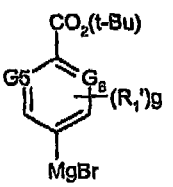
G5A



G5B



G5C

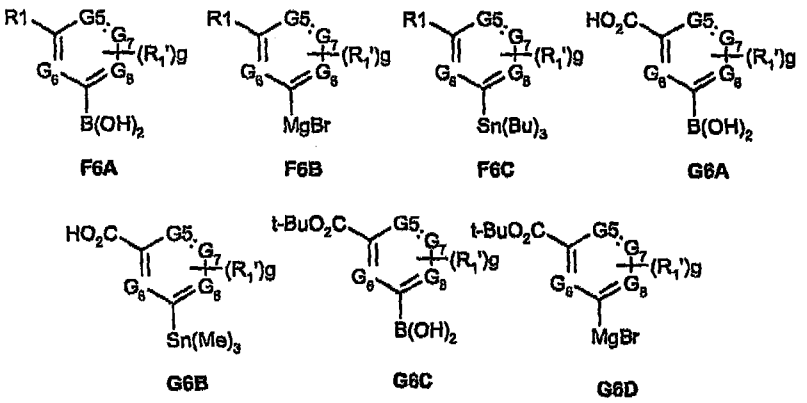


G5D

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Scheme 3 continued

Examples of Reagents in Method F & G for the Preparation of Compounds with Formula (VI) & (VIa)



F6A F6B F6C G6A

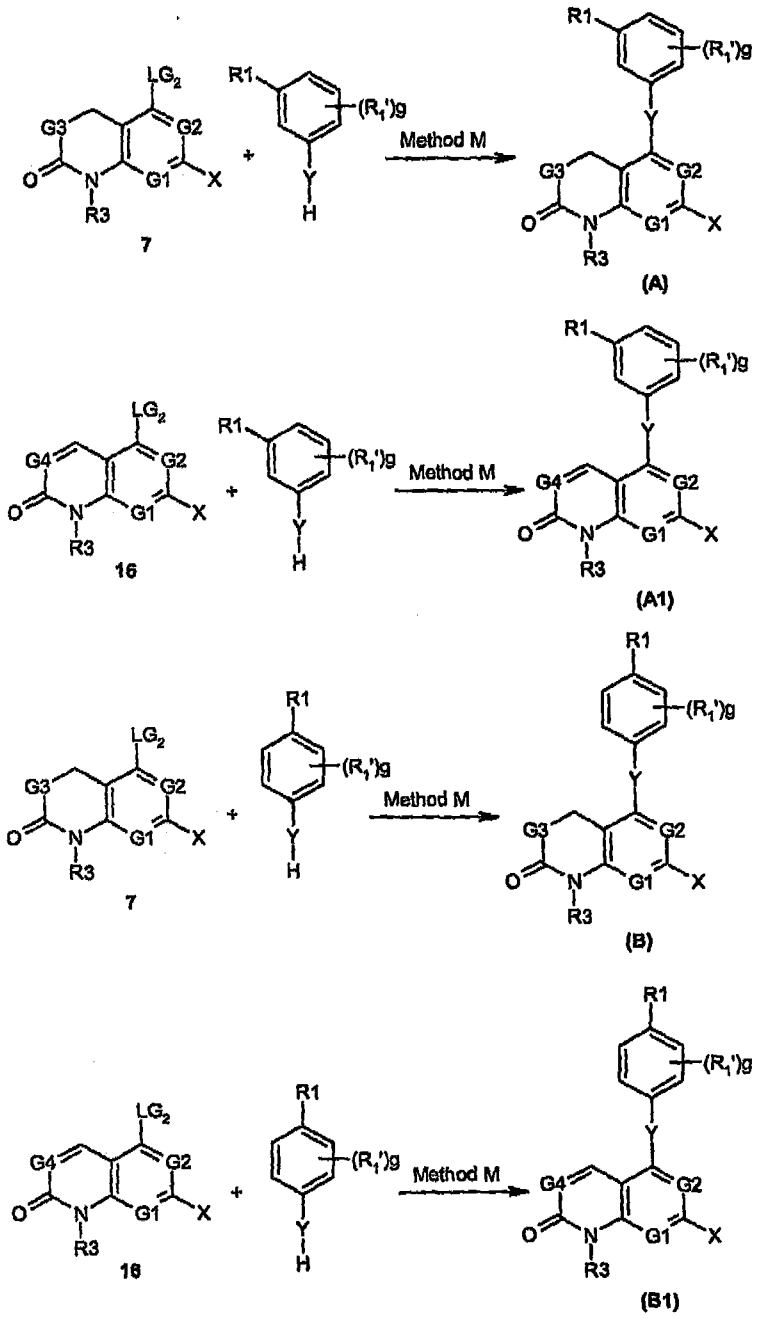
G6B G6C G6D

Preparation of compounds with Formula (A), (A1), (B) or (B1) can be achieved from appropriate intermediates in **Scheme 1 (or Scheme 2)** using proper synthetic methods known to the scientists with appropriate training in the literature. An example of these types of preparations is demonstrated, but not limited to, in **Scheme 4**. The preparation can be achieved by reacting compound **7** (for A or B) or **16** (for A1 or B1) with another reagent with appropriate structures as shown in **Scheme 4** employing Method M.

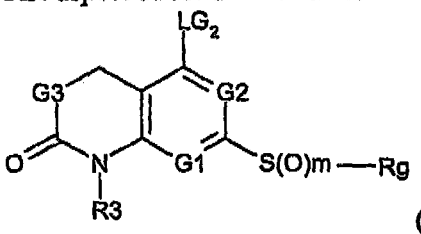
Method M is for the substitution of $-LG_2$ with appropriate compound containing the structural unit of -Y-H. This can be achieved by heating the reaction mixtures in appropriate solvents. The heating method can be selected from either a regular oil bath or microwave irradiations. Solvents can be CH_2Cl_2, DMSO, DMF, toluene, benzene, CH_3CN or NMP. The reaction may or may not require the presence of bases. An example of the base can be selected from, but not limited to triethyl amine, diisopropyl ethyl amine, NaH, *n*-BuLi, *tert*-BuLi, *tert*-BuOK, Li_2CO3, Cs_2CO_3 and pyridine. This transformation may also require the presence of catalytic amount of catalysts containing transition metals (e.g., Pd, Cu, Ni, or W). These catalysts include, but not limited to Pd/C, $Pd(PPh_3)_4$ and $PdCl_2$. Compounds that have $Y=S(O)_m$ or $S(O)_mC(R_y)(R_z)$ may also be prepared by the oxidation of their corresponding compounds with Y=S or $SC(R_y)(R_z)$. Suitable oxidation methods for use herein include, but not limited to mCPBA, Oxone, OsO_4, H_2O_2, potassium and zinc permanganate.

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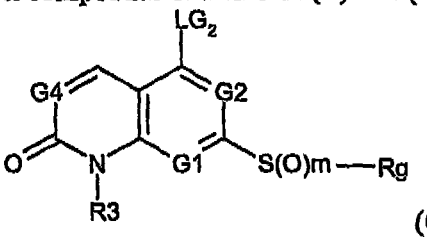
Scheme 4



One aspect of the invention are the novel compounds of Formula (C) and (C1):



(C)



(C1)

wherein,

G1, G2, G3 and G4 are as described for Formula (I) herein;

m is 0 or an integer having a value of 1 or 2;

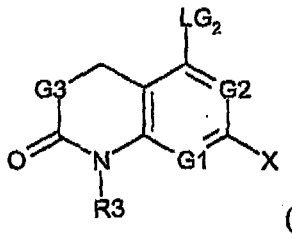
Rg is a C_{1-10}alkyl;

LG_2 is chlorine, bromine, iodine, or $O\text{-}S(O)_2CF_3$;

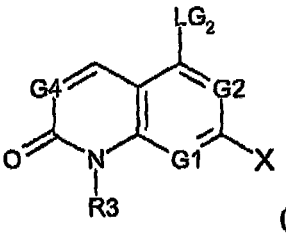
R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted (as defined for Formula (I) herein.

In one embodiment, Rg is methyl. In another embodiment, m is 0 or 1.

Another aspect of the invention are compounds of Formula (D) and (D1) represented by the structure:



(D)



(D1)

wherein,

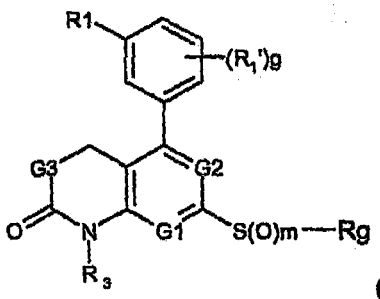
G1, G2, G3, G4 and X are as described for Formula (I) herein;

LG_2 is chlorine, bromine, iodine, or $O\text{-}S(O)_2CF_3$;

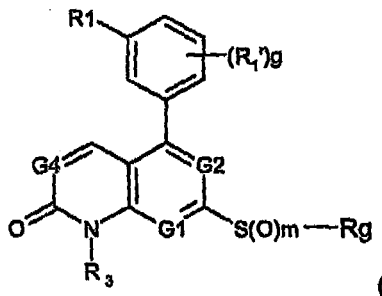
R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted (and as defined for Formula (I)).

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Another aspect of the invention are compounds of Formula (E) and (E1) represented by the structure:



(E) or



(E1)

wherein,

G1, G2, G3, G4, R_1 and $(R_1)_g$ are as described for Formula (I) herein;

m is 0 or an integer having a value of 1 or 2;

Rg is a C_{1-10}alkyl;

LG_2 is chlorine, bromine, iodine, or $O\text{-}S(O)_2CF_3$;

R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, aryl C_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted (as defined for Formula (I) herein.

Representative examples of Formula (E) and (E1) are:

3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid

N-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide

N-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide

3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide

N-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide

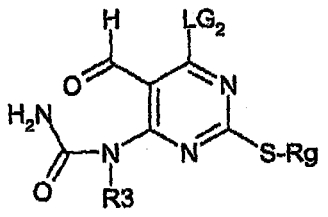
3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-

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[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide
3-[8-(2,6-Difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide
N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-d]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide
N-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide
3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-d]pyrimidin-4-yl]-N,N,4-trimethylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-*N*,4-dimethylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-*N*,4-dimethylbenzamide
3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid

It is also recognized that a similar set of formulas (F) and (F1) are contemplated when the R_1 moiety is substituted in the 3-position of the phenyl ring, as shown in compounds of Formula (II) and (IIa). Similar intermediates are also contemplated for the remaining Formulas herein wherein the C4 position of the pharmacophore is substituted with the various heteroaryl rings, e.g. G5/G6, etc. of the formulas described herein as Formula (III) and (IIIa), (IV) and (IVa), etc.

Another aspect of the invention are compounds of Formula (G):



(G)

wherein

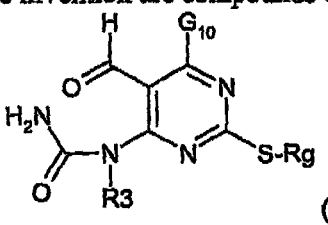
LG2 is chloro, bromo, iodo, O-S(O)$_2$CF$_3$;

Rg is an optionally substituted C$_{1-10}$ alkyl;

R3 is a C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, C$_{3-7}$ cycloalkyl C$_{1-10}$ alkyl, aryl, arylC$_{1-10}$ alkyl, heteroaryl, heteroarylC$_{1-10}$ alkyl, heterocyclic or a heterocyclylC$_{1-10}$ alkyl moiety, and wherein each of these moieties may be optionally substituted.

Suitably R$_3$ is substituted as defined herein for compounds of Formula (I).

Another aspect of the invention are compounds of Formula (H):



(H)

wherein

G10 is an aryl, aryl C$_{2-10}$ alkyl, heteroaryl, heteroaryl C$_{2-10}$ alkyl; aryl C$_{2-10}$ alkenyl, arylC$_{2-10}$ alkynyl, heteroaryl C$_{2-10}$ alkenyl, heteroaryl C$_{2-10}$ alkynyl, C$_{2-10}$alkenyl, or C$_{2-10}$ alkynyl moiety, which moieties may be optionally substituted with R$_1$ and (R$_1$')$_g$;

R$_1$ is C(Z)N(R$_{10}$')(CR$_{10}$R$_{20}$)$_v$R$_b$, C(Z)O(CR$_{10}$R$_{20}$)$_v$R$_b$, N(R$_{10}$')C(Z)(CR$_{10}$R$_{20}$)$_v$R$_b$; N(R$_{10}$')C(Z)N(R$_{10}$')(CR$_{10}$R$_{20}$)$_v$R$_b$; or N(R$_{10}$')OC(Z)(CR$_{10}$R$_{20}$)$_v$R$_b$;

R$_1$' is independently selected at each occurrence from hydrogen, halogen, C$_{1-4}$ alkyl, halo-substituted-C$_{1-4}$ alkyl, cyano, nitro, (CR$_{10}$R$_{20}$)$_{v'}$NR$_d$R$_{d'}$, (CR$_{10}$R$_{20}$)$_{v'}$C(O)R$_{12}$, SR$_5$, S(O)R$_5$, S(O)$_2$R$_5$, or (CR$_{10}$R$_{20}$)$_{v'}$OR$_{13}$;

R$_b$ is hydrogen, C$_{1-10}$ alkyl, C$_{3-7}$ cycloalkyl, C$_{3-7}$ cycloalkylC$_{1-10}$ alkyl, aryl, arylC$_{1-10}$alkyl, heteroaryl, heteroarylC$_{1-10}$ alkyl, heterocyclic, or

heterocyclylC_{1-10} alkyl moiety, which moieties excluding hydrogen, may all be optionally substituted;

R_5 is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or $NR_4'R_{14}'$, excluding the moieties SR_5 being $SNR_4'R_{14}'$, $S(O)_2R_5$ being SO_2H and $S(O)R_5$ being SOH;

R_4' and R_{14}' are each independently selected at each occurrence from hydrogen or C_{1-4} alkyl, or R_4' and R_{14}' together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members, which ring optionally contains an additional heteroatom selected from NR9';

R_d and R_d' are each independently selected at each occurrence from hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylC_{1-4}alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted; or R_d and R_d' together with the nitrogen which they are attached form an optionally substituted heterocyclic ring of 5 to 6 members, which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9';

R9' is independently selected at each occurrence from hydrogen, or C_{1-4} alkyl;

R_{10} and R_{20} are independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{10}' is independently selected at each occurrence from hydrogen or C_{1-4}alkyl;

R_{12} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

R_{13} is independently selected at each occurrence from hydrogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, C_{5-7} cycloalkenyl, C_{5-7}cycloalkenyl C_{1-4} alkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4} alkyl, heterocyclyl, or a heterocyclylC_{1-4} alkyl moiety, and wherein each of these moieties, excluding hydrogen, may be optionally substituted;

v is 0 or an integer having a value of 1 or 2;

v' is independently selected at each occurrence from 0 or an integer having a value of 1 or 2;

Z is independently selected at each occurrence from oxygen or sulfur;

Rg is an optionally substituted C_{1-10} alkyl;

R_3 is a C_{1-10} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-10} alkyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, heterocyclic or a heterocyclylC_{1-10} alkyl moiety, and wherein each of these moieties may be optionally substituted.

Suitably R_3 is substituted as defined herein for compounds of Formula (I).

Compounds of Formula (H) may be made by reacting the compound disclosed as structure 4 in Scheme I found in WO 02/059083 with a suitably substituted isocyanate, such as $ClS(O)_2NCO$, or TMS -NCO in a aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine, followed by reaction with ammonia; or by reacting structure 4 with phosgene in an aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine, followed by reaction with ammonia or by reacting structure 4 with $COCl_2$ or methylchloroformate or other chloroformates in an aprotic organic solvent, such as toluene, methylene chloride, chloroform, benzene, THF, hexane, optionally with a non-nucleophilic base, such as triethylamine, diisopropyl ethylamine, pyridine, followed by reaction with ammonia. This reaction may, or may not, require heating (e.g, temperature between r.t. and 250 °C). The heating can be carried out in any manner and may include the use of an oil bath or microwave irradiation.

Experimentals

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an Ar atmosphere where necessary.

List of Abbreviations

DMAP: 4-(Dimethylamino)pyridine	SPE: Solid phase extraction
DCM: Dichloromethane	m-CPBA: 3-Chlorobenzene-carboperoxoic acid
DMF: *N,N*-Dimethylformamide	MDAP: Mass directed auto preparation
dppf: 1,1'-Bis(diphenylphosphino)-ferrocene	NIS: *N*-Iodosuccinimide
DMSO: Dimethylsulfoxide	HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
DIPEA: *N,N*-Diisopropylethylamine	HBTU: *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
DSC: differential scanning calorimetry	HOBT: 1-Hydoxybenzotriazole hydrate
EtOAc: Ethyl acetate	IPA: isopropyl alcohol
EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride	THF: Tetrahydrofuran
TFA: Trifluoroacetic anhydride	mol: moles
M: molar	mmol: millimoles
L: liters	satd: saturated
mL: milliliters	eq: equivalents
g: grams	min: minutes
mg: milligrams	mp: melting point
h: hours	rt: room temperature
Aq: aqueous	NMP = 1-methyl-2-pyrrolidinone

LC-MS Experimental Conditions:

Liquid Chromatograph

System: Shimadzu LC system with SCL-10A Controller and dual UV detector

Autosampler: Leap CTC with a Valco six port injector

Column: Aquasil/Aquasil (C18 40x1 mm)

Inj. Vol.(uL): 2.0

Solvent A: H_2O, 0.02% TFA

Solvent B: MeCN, 0.018% TFA

Gradient: linear

Channel A: UV 214 nm

Channel B: ELS

Step	Time (min)	Dura.(min)	Flow (µL/min)	Sol.A	Sol.B
0	0.00	0.00	300.00	95.00	5.00
1	0.00	0.01	300.00	95.00	5.00
2	0.01	3.20	300.00	10.00	90.00
3	3.21	1.00	300.00	10.00	90.00
4	4.21	0.10	300.00	95.00	5.00
5	4.31	0.40	300.00	95.00	5.00

Mass Spectrometer: PE Sciex Single Quadrupole LC/MS API-150

Polarity: Positive

Acquisition mode: Profile

General Procedures

Nuclear magnetic resonance spectra were recorded at 400 MHz using on a Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD (or MeOD) is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or the NMR solvent. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Mass spectra were taken on a instruments, using electrospray (ES) ionization techniques. All temperatures are reported in degrees Celsius. All other abbreviations are as described in the ACS Style Guide (American Chemical Society, Washington, DC, 1986).

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography

were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Preparative hplc were performed using a Gilson Preparative System using a Luna 5u C18(2) 100A reverse phase column eluting with a 10-80 gradient (0.1%TFA in acetonitrile/0.1% aqueous TFA) or a 10-80 gradient (acetonitrile/water). The CombiFlash system used for purification in this application was purchased from Isco, Inc. CombiFlash purification was carried out using a prepacked SiO_2 column, a detector with UV wavelength at 254nm and mixed solvents.

Heating of reaction mixtures with microwave irradiations was carried out on a Smith Creator (purchased from Personal Chemistry, Forboro/MA, now owned by Biotage), a Emrys Optimizer (purchased from Personal Chemistry) or an Explorer (provided by CEM Discover, Matthews/NC) microwave.

General Procedure for Sulfoxide/Sulfone Displacement

The sulfoxide/sulfone of the template is dissolved in THF/$CHCl_3$ (1:1) and the amine (5 eq) and diisopropylehtylamine (3 eq) are added and allowed to stir for 1h. The mixture is concentrated *in vacuo*.

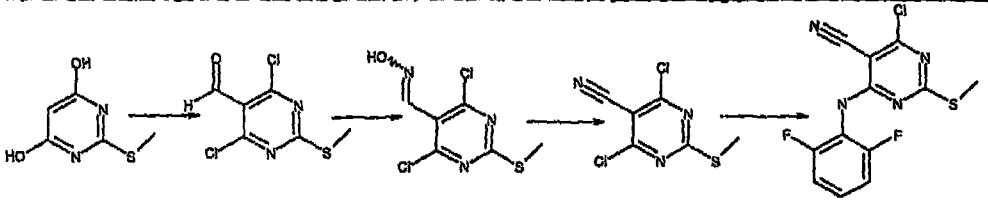
General Procedure for HATU Couplings

The acid is dissolved in DMF and HATU (1 eq) is added. DIEA is added (2 eq) followed by the amine (1.1 eq) and allowed to stir for 18h. The reaction mixture is concentrated and redissolved in $CHCl_3$.

Example 1

3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-cyclobutyl-4-methylbenzamide

1a) 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile



To the solution of phosphorus oxychloride (65 mL, 0.70 mol) in trichloroethylene (46.5 mL) was added DMF (25 mL, 0.32 mol) slowly to keep the temperature between 5 °C to 10 °C. The solution was then warmed up to room temperature before 6-hydroxy-2-(methylthio)-4(1*H*)-pyrimidinone (25 g, 0.16 mol) was added in portions. The resultant reaction mixture was heated at 80 °C overnight followed by concentration under vacuum. The resulting slurry like residue was poured into ice, stirred for about 2 hours then filtered to afford the crude product.

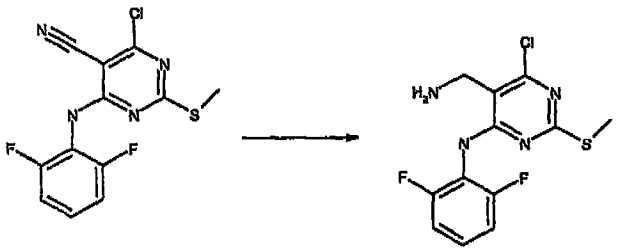
The crude product was further purified by recrystalization with hexane to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (21.3 g , 61%). ^{1}H-NMR ($CDCl_3$) δ 2.66 (s, 3 H), 10.4 (s, 1 H).

To the mixture of hydroxylamine hydrochloride (139 mg, 2.0 mmol), HOAc (0.113 mL, 2.0 mmol) and EtOH (5 mL) was added 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde (223 mg, 1.0 mol) to room temperature. The solution was then heated at 50 °C for about 1 hour, 60 °C for about 30 minutes and 70 °C for about 30 minutes before it was concentrated under vacuum and washed with H_2O (10-20 mL) to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde oxime (190 mg, 80%). LC-MS *m/z* 238 $(M + H)^+$ 1.57 minute, 1.65 minute; ^{1}H-NMR ($CDCl_3$) δ 2.62, 2.65 (3 H), 7.53, 8.30 (1 H).

To 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbaldehyde oxime (2.38 g, 10 mmol) was added $SOCl_2$ (21.8 mL, 0.30 mol) slowly at room temperature. The solution was then heated at 75 °C for about 3 hours before it was concentrated under vacuum. The residue $SOCl_2$ was removed by evaporation with toluene (5 mL) under vacuum. The resulting solid was washed with EtOH/H_2O (10mL, 1 : 1) to afford 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbonitrile (2.04 g, 93%). LC-MS *m/z* 220 $(M + H)^+$1.99 minute; ^{1}H-NMR ($CDCl_3$) δ 2.64(3 H).

To the solution of 4,6-dichloro-2-(methylthio)-5-pyrimidinecarbonitrile (2.20 g, 10.0 mmol) in DMF (10 mL) was added 2,6-difluoroaniline (2.17 mL, 20.0 mmol). The solution was stirred at 50 °C for about 60 minutes. The mixture was slowly added into a solution of MeOH (20 mL) and water (30 mL). The resultant solid was filtered and washed with MeOH / H_2O (20 mL, 1:1) to give 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile as a white solid (2.82 g, 90 %). LC-MS *m/z* 313 $(M + H)^+$; ^{1}H-NMR ($CDCl_3$) δ 2.33 (s, 3 H), 6.94 (s, 1 H), 7.04 (m, 2 H), 7.35 (m, 1 H).

1b) 5-(Aminomethyl)-6-chloro-*N*-(2,6-difluorophenyl)-2-(methylthio)-4-pyrimidinamine



To the solution of 4-chloro-6-[(2,6-difluorophenyl)amino]-2-(methylthio)-5-pyrimidinecarbonitrile (0.938 g) was added borane•THF complex (1.0 M, 15 mL). The reaction mixture was then heated at reflux for about 4 h until all the starting

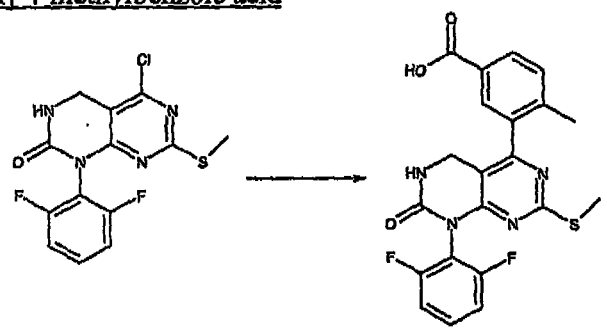
material disappeared. The solution was cooled to r.t., mixed with HCl solution (6 M, 5 mL), and stirred at room temperature for about 30 minutes. The solution was then mixed with NaOH solution (3 M) to pH 9.0-10.0. The organic phase was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), collected, dried over Na_2SO_4 and concentrated to afford the title compound 0.97 g (quantative). LC-MS *m/z* 317 $(M+H)^+$, 1.5 min (ret. time).

1c) 5-Chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To the solution of 5-(aminomethyl)-6-chloro-*N*-(2,6-difluorophenyl)-2-(methylthio)-4-pyrimidinamine (0.317 g) in CH_2Cl_2 (5 mL) was added the mixture of carbonyl diimidazole (0.178 g) in CH_2Cl_2 (5 mL). The resultant mixture was stirred for about 3 hours at r.t., mixed with CH_2Cl_2 (10 mL) and washed with HCl (1 N, 2 x 10 mL) and H_2O (20 mL). The organic layers were collected, dried over Na_2SO_4, filtered and concentrated to provide the title compound (0.279 g, 81%). LC-MS *m/z* 343 $(M+H)^+$, 1.75 min (ret. time); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44-7.40 (m, 1H), 7.07-7.03 (m, 2H), 5.84 (br, 1H), 4.62 (s, 2H), 2.19 (s, 3H).

1d) 3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid

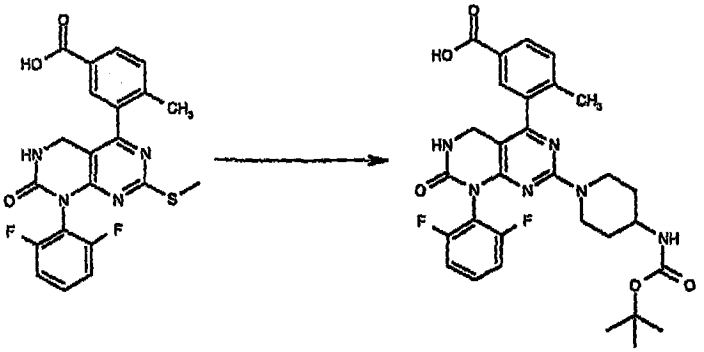


To a stirring solution of 3-iodo-4-methylbenzoic acid (60 g, 0.22 mol, 1 eq) in degassed DMF (1400 mL, 23.3 vol.) was charged 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (81.4 g, 0.32 mol, 1.4 eq) followed by potassium acetate

(112 g, 1.14 mole, 5eq) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (18.7 g, 0.02 mole, 0.1eq). The resulting mixture was placed under a nitrogen atmosphere and was heated to 80 °C with the exclusion of light overnight. The mixture was then concentrated under high vacuum and the residue partitioned between EtOAc and 2M HCl. The mixture was then filtered and the layers separated. The aqueous phase was re-extracted with EtOAc. The combined organics were then washed with brine, dried and evaporated to yield a brown solid that was applied to a silica plug then eluted with 2:1 cyclohexane : ethyl acetate. Fractions were then combined and evaporated to yield a brown foam that was triturated with cyclohexane, collected by filtration then dried in *vacuo* to yield 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid. δ ($CDCl_3$) 8.50-8.49 (1H, d), 8.04-8.02 (1H, dd), 7.27-7.25 (1H, d), 2.61 (3H, s), 1.36 (12H, s)

5-Chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.58 mmol) was mixed with 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (0.23 g), K_2CO_3 (0.485 g), dioxane (18 mL) and H_2O (6 mL). The resultant mixture was passed through by a stream of argon for 10 min, mixed with $Pd(PPh_3)_4$ (34 mg) and heated at 150 °C for 1 h. It was filtered through celite, mixed with 1 mL acetic acid and washed with brine. The organic layers were collected, dried over $MgSO_4$, filtered and concentrated and the residue was purified by flash column chromatography to provide the title compound (160 mg). LC-MS *m/z* 443.2 $(M+H)^+$, 1.98 min (ret. time).

1e) 3-{8-(2,6-Difluorophenyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylbenzoic acid

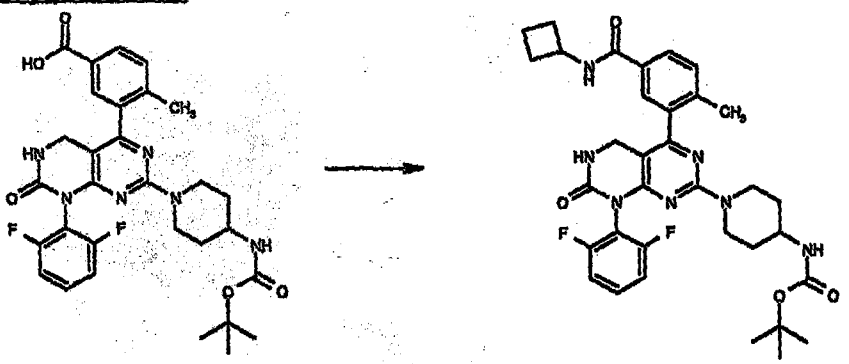


To the solution of the title compound from Example 1d (100 mg) in methylene chloride (20 mL) was added m-CPBA (80 mg) at r.t, followed by 1 mL of MeOH. The reaction mixture was stirred for overnight, diluted with EtOAc, and

washed with 5% Na_2CO_3, H_2O and brine. The organic phases were collected, dried over $MgSO_4$, concentrated to afford the mixture of sulfone and sulfoxide as a yellow solid that was used without further purification.

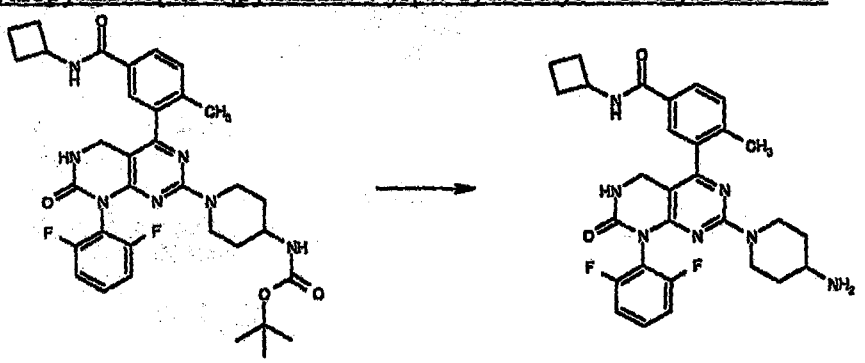
To the solution of the above sufoxide and sulfone mixture in THF (20 mL) was added 1,1-dimethylethyl 4-piperidinylcarbamate (200 mg). The reaction mixture was heated at reflux for 4 h. The solution was then evaporated *in vacuo* and the residue was purified via flash column chromatography to provide the title compound as a white solid. LC-MS *m/z* 595.4 $(M+H)^+$, 2.18 min (ret. time).

1f) 1,1-Dimethylethyl {1-[4-{5-[(cyclobutylamino)carbonyl]-2-methylphenyl}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]-4-piperidinyl}carbamate



To the solution of the compound from Example 1d (200 mg) in methylene chloride (100 mL) were added EDC (80 mg), HOBt (60 mg) and cyclobutylamine (100 uL) at r.t. The reaction mixture was stirred overnight and evaporated *in vacuo*. Flash chromatography afforded the title compound as a white solid. LC-MS *m/z* 648 $(M+H)^+$, 2.36 min (ret. time).

1g) 3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-cyclobutyl-4-methylbenzamide

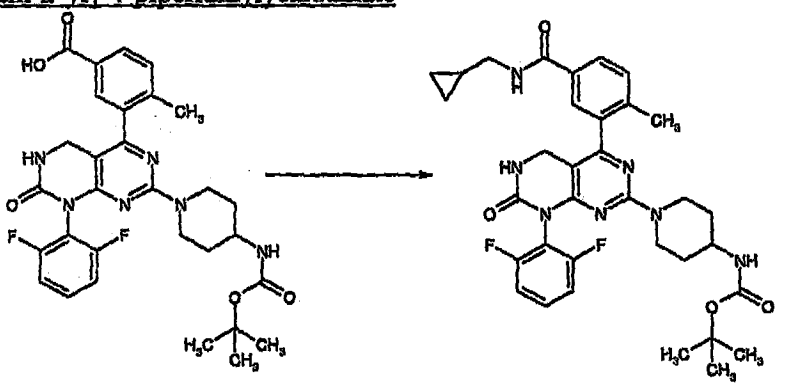


To the solution of the title compound from Example 1f (50 mg) in CH_2Cl_2 (5 mL) was added TFA (1 mL) at r.t. The reaction mixture was stirred at r.t. for 3 h and concentrated. It was mixed with EtOAc (5 mL) and washed with 1 M NaOH solution (5 mL), followed by brine. The organic part was collected, dried over K_2CO_3 and concentrated *in vacuo* to afford the free base of the title compound as a white solid. LC-MS *m/z* 548 $(M+H)^+$, 1.61 min (ret time).

Example 2

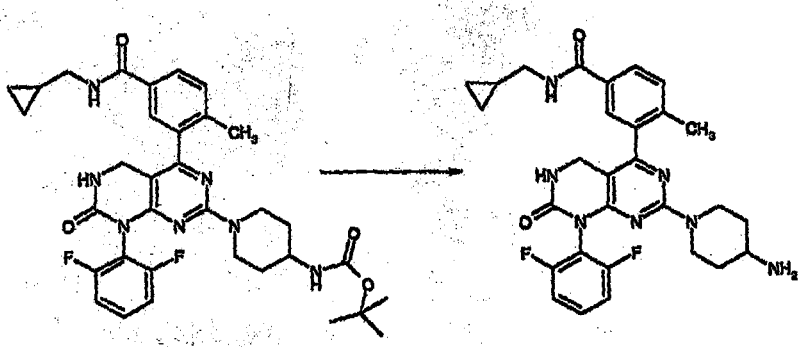
3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(cyclopropylmethyl)-4-methylbenzamide

2a) 1,1-Dimethylethyl {1-[4-(5-{[(cyclopropylmethyl)amino]carbonyl}-2-methylphenyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]-4-piperidinyl}carbamate



To a solution of 3-{8-(2,6-Difluorophenyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylbenzoic acid (250 mg) in methylenechloride (100 mL) were added EDC (100 mg), HOBt (70 mg) and cyclopropylmethylamine (110 uL). The reaction was stirred at r.t. overnight and evaporated *in vacuo*. Flash chromatography then provided the title compound as a white solid. LC-MS *m/z* 648 $(M+H)^+$, 2.33 min (ret. time).

2b) 3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(cyclopropylmethyl)-4-methylbenzamide

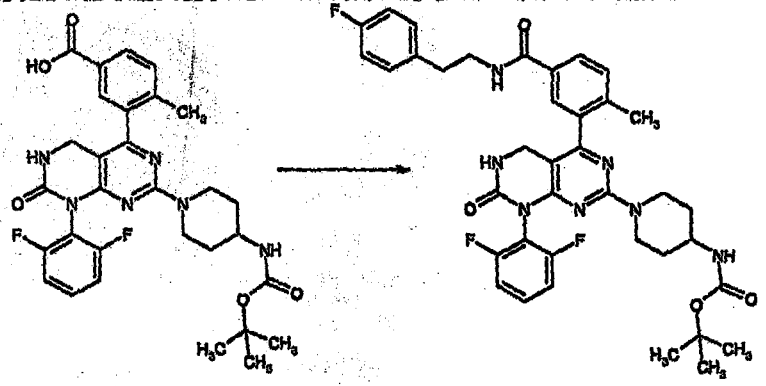


To a solution of the title compound from Example 2a (50 mg) in CH_2Cl_2 (5 mL) was added TFA (1 mL) at r.t. The reaction mixture was stirred for 3 h and concentrated *in vacuo*. The residue was mixed with EtOAc (5 mL) and NaOH solution (1 M, 5 mL). The organic part was separated, washed with brine, dried over K_2CO_3 and concentrated *in vacuo* to yield the free base of the title compound as a white solid. LC-MS *m/z* 548 $(M+H)^+$, 1.52 min (ret. time).

Example 3

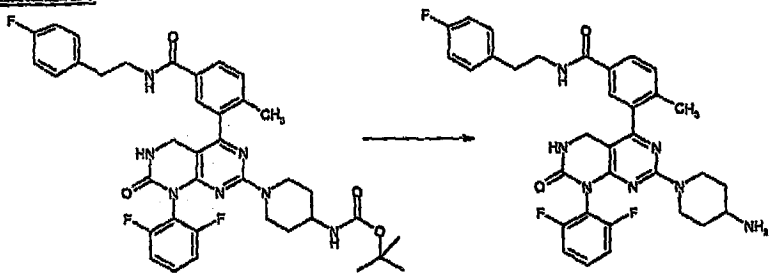
3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-*N*-[2-(4-fluorophenyl)ethyl]-4-methylbenzamide

3a) 1,1-Dimethylethyl (1-{8-(2,6-difluorophenyl)-4-[5-({[2-(4-fluorophenyl)ethyl]amino}carbonyl)-2-methylphenyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl}-4-piperidinyl)carbamate



The title compound was prepared from 3-{8-(2,6-Difluorophenyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylbenzoic acid by following the procedures in Example 1f except using 4-fluorophenylethylamine for the amide formation. LC-MS *m/z* 716 $(M+H)^+$, 2.47 min (ret. time).

3b) 3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-*N*-[2-(4-fluorophenyl)ethyl]-4-methylbenzamide

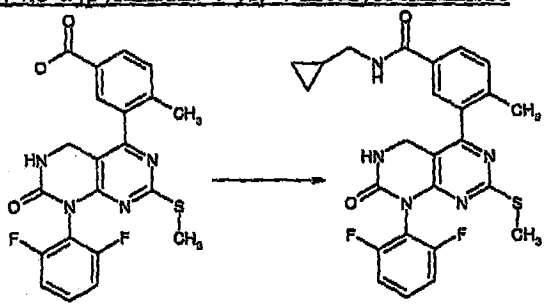


The title compound was prepared from the compound from Example 3a by following the procedures in Example 1g. LC-MS *m/z* 616 $(M+H)^+$, 1.69 min (ret. time).

Example 4

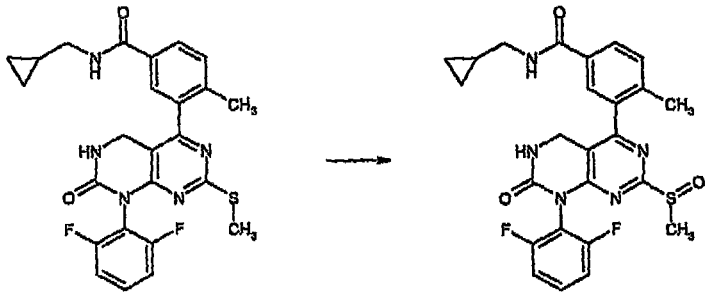
3-[2-[(2-Aminoethyl)(methyl)amino]-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(cyclopropylmethyl)-4-methylbenzamide

4a) *N*-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide



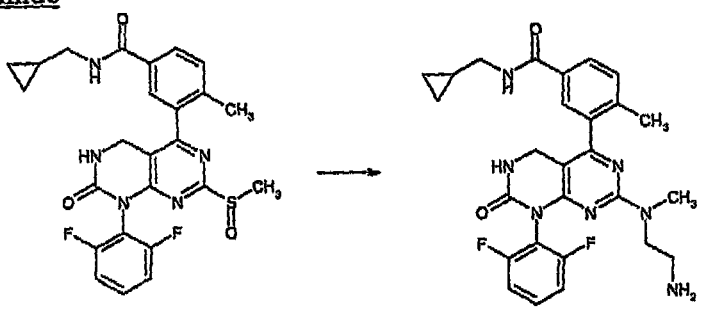
To a solution of 3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (500 mg) in methylenechloride (100 mL) were added EDC (260 mg), HOBt (160 mg) and cyclopropylmethylamine (260 uL). The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was purified via column chromatography to provide the title compound as a white solid. LC-MS *m/z* 496 $(M+H)^+$, 2.62 min (ret. time).

4b) *N*-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide



To the solution of the compound from Example 4a (500 mg) in methylenechloride (20 mL) and methanol (10 mL) was added m-CPBA (200 mg) at r.t. The reaction mixture was stirred for 0.5 h and filtered through a silica plug. The solution was dried over $MgSO_4$ and concentrated to afford the title compound as a yellow solid that was used without further purification. LC-MS *m/z* 512 $(M+H)^+$, 1.77 min (ret time).

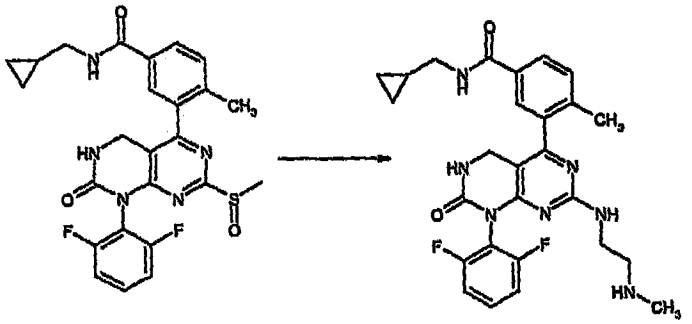
4c) 3-[2-[(2-Aminoethyl)(methyl)amino]-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(cyclopropylmethyl)-4-methylbenzamide



To the solution of the compound from Example 4b (90mg) in THF (10 mL) was added *N*-methyl ethylene diamine (70 uL) at r.t. The reaction mixture was stirred at r.t. overnight. The solution was then evaporated *in vacuo* and the residue was purified by column chromatography to provide the title compound as a white solid. LC-MS *m/z* 522 $(M+H)^+$, 1.55 min (ret. time).

Example 5

N-(Cyclopropylmethyl)-3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methylbenzamide

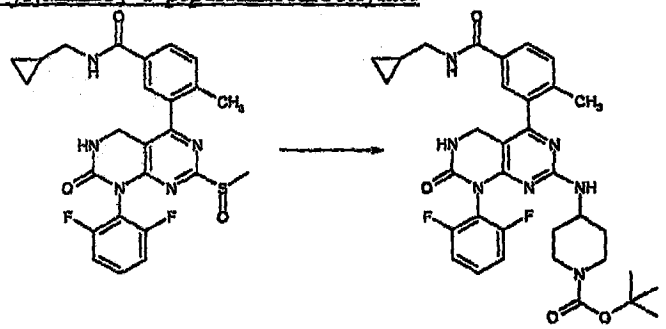


To the solution of *N*-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide (90mg) in THF (10 mL) was added *N*-methyl ethylene diamine (70 uL) at r.t. The reaction mixture was stirred at r.t. overnight. The solution was then evaporated *in vacuo* and the residue was purified by column chromatography to provide the title compound as a white solid (in addition to compound 4c). LC-MS *m/z* 522 $(M+H)^+$, 1.47 min (ret. time).

Example 6

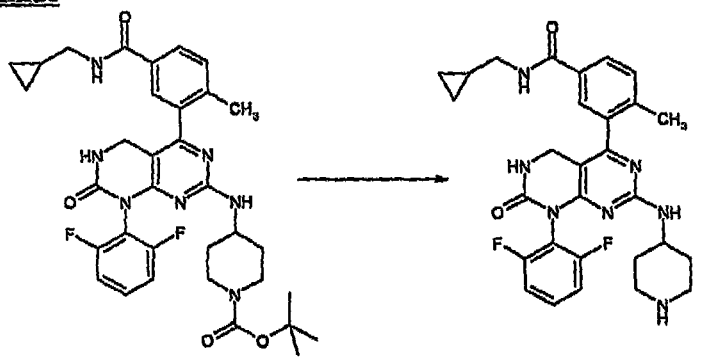
N-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide

6a) 1,1-Dimethylethyl 4-{[4-(5-{[(cyclopropylmethyl)amino]carbonyl}-2-methylphenyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate



To the solution of *N*-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide (100 mg) in THF (10 mL) was added 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (195 mg) at r.t. The reaction mixture was heated at reflux for 4 h. The solution was then evaporated *in vacuo* and the residue was purified by column chromatography to provide the title compound as a white solid. LC-MS *m/z* 648.4 $(M+H)^+$, 2.16 min (ret. time).

6b) *N*-(Cyclopropylmethyl)-3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzamide

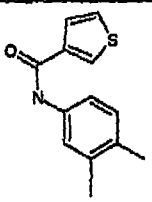


To the solution of the compound from Example 6a (50 mg) in CH_2Cl_2 (5 mL) was added 1 mL of TFA at r.t. The reaction solution was stirred at r.t. for 3 h and concentrated *in vacuo*. The resultant residue was mixed with EtOAc (5 mL) and NaOH solution (1 M, 5 mL). The organic part was separated, washed with brine, dried over K_2CO_3 and concentrated *in vacuo* to yield the free base of the title compound as a white solid. LC-MS *m/z* 548 $(M+H)^+$, 1.46 min (ret. time).

Example 7

N-(3-{8-(2,6-Difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-thiophenecarboxamide

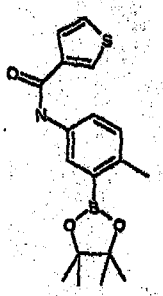
7a) *N*-(3-iodo-4-methylphenyl)-3-thiophenecarboxamide



3-Thiophenecarboxylic acid (2.0 g, 15.6 mmol) was dissolved in methylene chloride (100 mL) and 2 drops of DMF were added. The mixture was cooled to 0 °C and oxalyl chloride (1.5 mL, 17.1 mmol) was added slowly and allowed to warm to room temperature. Gas evolution was observed during warming. 3-Methyl-4-iodoaniline (5.45 g, 23.5 mmol), 4 drops of pyridine and K_2CO_3 (2.58 g, 18.7 mmol) are dissolved in CH_2Cl_2 (10 mL) and cooled to about 0 °C. After about 1h, the acid chloride mixture is slowly added to the cooled aniline mixture and allowed to warm to room temperature and stirred for about 18h. The resulting mixture is filtered, washed with ethyl acetate and the filtrate is concentrated to a brown oil. The crude

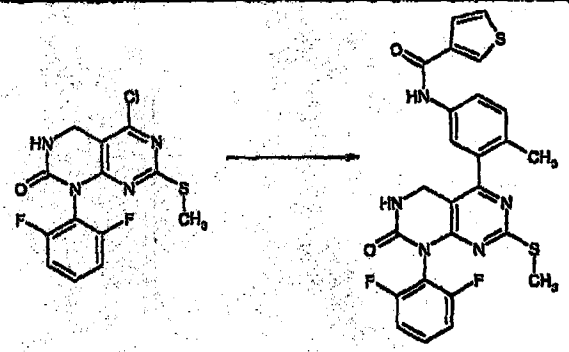
material was purified via flash chromatography (10-30% ethyl acetate in hexanes) to afford the title compound (1.56 g, 29%) as an off-white solid.

7b) *N*-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-thiophenecarboxamide



The iodide from Example 7a (1.56 g, 4.5 mmol), bis(pinacolato)diboran (2.3 g, 9.0 mmol), potassium acetate (2.21 g, 22.5 mmol) and $PdCl_2$.dppf (0.15 g, 0.225 mmol) are dissolved in DMF (50 mL) and heated to about 85 °C for about 24 h. The mixture was then concentrated to an oil and ethyl acetate and water were added. The organic portion was washed with brine and dried (Na_2SO_4). The concentrated organic layer was purified via flash chromatography to give the title compound (0.212 g, 13%).

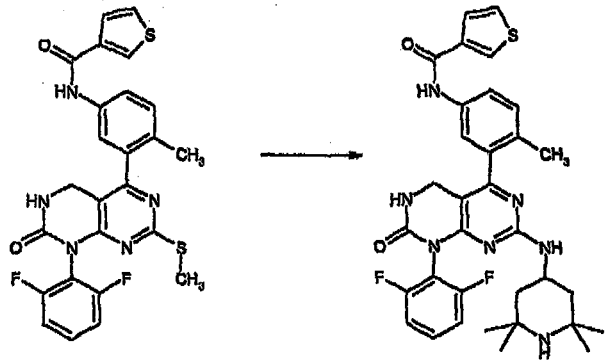
7c) *N*-{3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The title compound was prepared from 5-Chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one by following the procedures in Example 1d except using *N*-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-thiophenecarboxamide for the Suzuki cross-coupling reaction. LC-MS *m/z* 524 $(M+H)^+$, 2.21 min (ret. time).

7d) *N*-(3-{8-(2,6-Difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-

methylphenyl)-3-thiophenecarboxamide



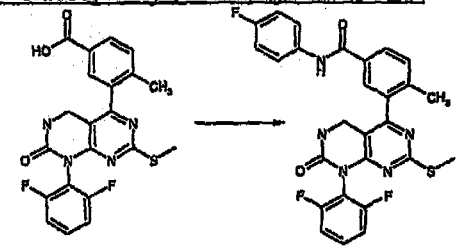
To the solution of the compound from Example 7c (83 mg) in methylenechloride (10 mL) was added m-CPBA (41 mg) and MeOH (1 mL). The reaction solution was stirred overnight, diluted with EtOAc, and washed with 5% Na_2CO_3, H_2O and brine. The organic part was separated, dried over $MgSO_4$, concentrated to afford the mixture of sulfone and sulfoxide as a yellow solid that was used without further purification.

To the solution of the above sufoxide and sulfone mixture in THF (10 mL) was added 2,2,6,6-tetramethyl-4-piperidinamine (123 uL). The reaction mixture was heated at reflux for 4 h and concentrated *in vacuo*. Flash chromatography then provided the title compound as a white solid. LC-MS m/z 632.6 $(M+H)^+$, 1.68 min (ret. time).

Example 8

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl)-N-(4-fluorophenyl)-4-methylbenzamide

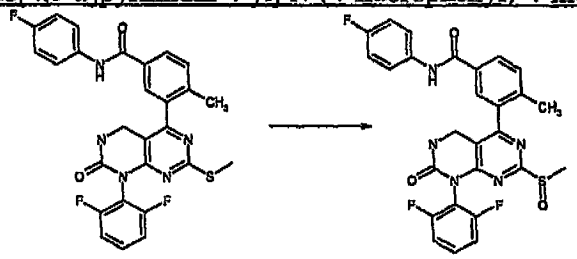
8a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (1.2 g, 2.71 mmol) in CH_2Cl_2 (80 mL) were added diisopropyl ethyl amine (0.96 mL, 5.5 mmol), HATU (1.044 g, 2.75 mmol) and 4-floroaniline (0.276 mL, 2.92 mmol). The

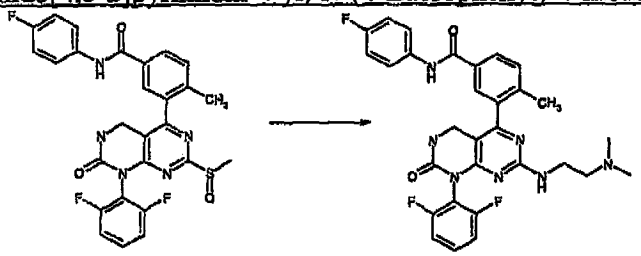
reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL) and shaked. The layers were separated and the organic layer was washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (load column with DCM, mobile phase EtOAc/Hexane) then provided the title compound as a white solid 1.33 g (92 %). LC-MS m/z 536 $(M + H)^+$.

8b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of the title compound from Example 8a (100 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (45 mg, 0.20 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. CombiFlash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 90 mg (87 %). LC-MS m/z 552 $(M + H)^+$.

8c) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide

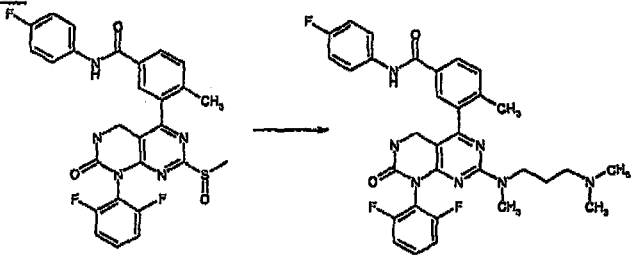


To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (300 mg, 0.54 mmol) in CH_2Cl_2 (30 mL) were added diisopropyl ethyl amine (0.2 mL, 1.14 mmol), N,N-dimethyl-ethylenediamine (0.3 mL, 2.7 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (131 mg, 42 %). LC-MS m/z 576 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.19 (s, 6 H),

2.35 (s, 3 H), 2.42 (m, br, 2H), 3.24 (m, br, 2 H), 4.16 (s, 2 H), 7.12 (m, 4 H), 7.52 (m, 2 H), 7.72 (m, 2 H), 7.83 (s, 1 H), 7.99 (d, 1 H).

Example 9

3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)-propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl}-N-(4-fluorophenyl)-4-methylbenzamide

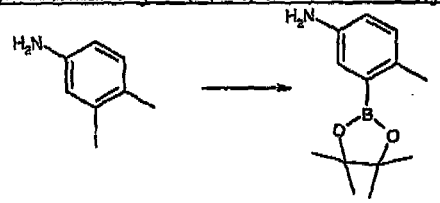


The title compound was prepared from compound from Example 8b by following the procedures in Example 8c except using N,N,N'-trimethyl-1,3-propanediamine for the displacement reaction. LC-MS *m/z* 604.2 $(M+H)^+$, 1.77 min (ret. time); ^{1}H-NMR(MeOD) δ 1.60 (m, 2H), 2.10 (m, 2H), 2.19 (s, 6H), 2.35 (s, 3H), 2.98 (m, 3H), 3.33 (m, 2H), 4.18 (s, 2H), 7.17 (m, 4H), 7.53 (m, 2H), 7.77 (m, 2H), 7.83 (s, 1H), 7.98 (d, 1H).

Example 10

N-{3-[8-(2,6-difluorophenyl)-2-(methyloxy)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide

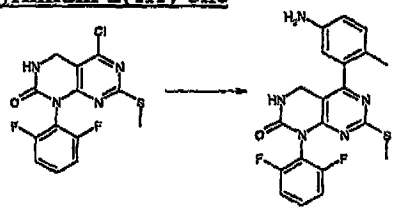
10a) 4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



3-Iodo-4-methylaniline (11 g, 47.2 mmol), bis(pinacolato)diboron (24.25 g, 95.5 mmol) and potassium acetate (14.3 g, 145.7 mmol) were stirred under argon in DMF (250 mL) in an oil bath maintained at 80°C. The mixture was degassed by vigorously bubbling argon through the mixture for 5 minutes. Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (1.875 g, 2.3 mmol) was added and the mixture heated at 80°C while stirring under argon for 17 hours. The mixture was allowed to cool to room temperature and 50 g of silica gel were added. Most of the solvent was pumped off *in vacuo*. The residue was flash chromatographed on 200 grams of silica gel eluted with 0-15% ethyl

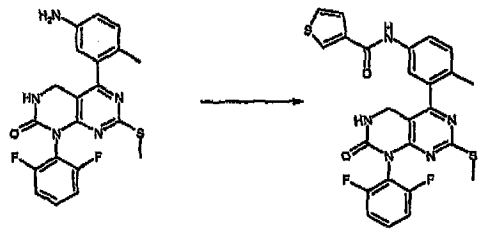
acetate/hexane to give the title compound as a light yellow solid. LC- MS *m/z* 233 $(M)^+$,1.53 min (ret. time).

10b) 5-(5-Amino-2-methylphenyl)-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To 5-chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (0.342 g, 1 mmol) and 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.256 g, 1.1 mmol) in dioxane (40 mL), was added a solution of K_2CO_3 (0.417 g, 3 mmol) in water (10 mL). Argon was vigorously bubbled through the mixture for 5 minutes and then tetrakis(triphenyl-phosphine)palladium(0) (0.078 g, 0.05 mmol) was added. The mixture was heated in a 95°C oil bath for 17 hours. The solvent was pumped off *in vacuo*, and the residue partitioned between ethyl acetate and water. The phases separated and the organic phase washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was flash chromatographed on silica gel (20 grams) eluted with 0-10% MeOH/CH_2Cl_2 to give the title product as a white solid. mp 122-125°C. LC-MS *m/z* 414 $(M+H)^+$,1.58 min (ret. time).

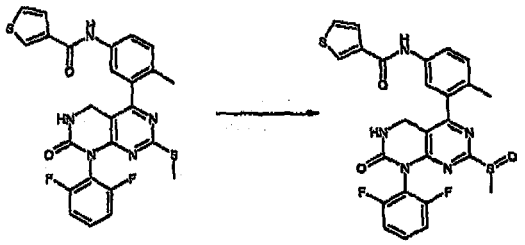
10c) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The compounds 5-(5-amino-2-methylphenyl)-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (0.205 g, 0.5 mmol), 3-thiophenecarboxylic acid (0.0647 g, 0.5 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.107 g, 0.55 mmol), 4-(dimethylamino)pyridine (0.002 g, 0.016 mmol), and triethylamine (0.14 mL, 1 mmol), were dissolved in

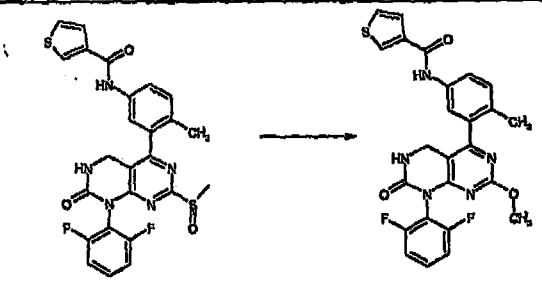
chloroform (10 mL) and stirred under argon at room temperature for 16 h. The reaction was not complete. An additional 3-thiophenecarboxylic acid (0.13 g, 1.0 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.107 g, 0.55 mmol) were dded and heated to 40°C for 17 h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water (3x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was flash chromatographed on silica gel (10 g) eluted with 0-5% MeOH/ CH_2Cl_2 to give the title compound as a solid. LC-MS *m/z* 524 $(M+H)^+$, 2.2 min (ret. time).

10d) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophene-carboxamide (0.052 g, 0.1 mmol) was dissolved in a mixture of CH_2Cl_2 (10 mL) and DMF (0.5 mL). Then 3-chloroperoxybenzoic acid (50-60%) (0.03 g, ~0.1 mmol) was added and the mixture stirred for 45 min at room temperature. Solvent was pumped off *in vacuo* to give the title compound plus a small amount of the corresponding sulfone. The mixture was used without further purification. LC-MS m/z 540 $(M+H)^+$, 1.76 min (ret. time).

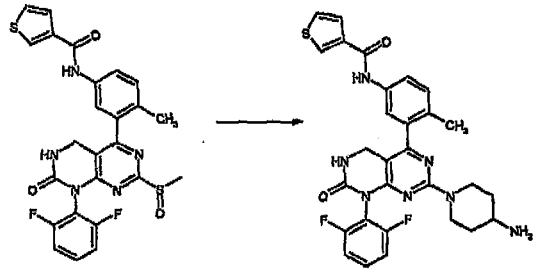
10e) *N*-{3-[8-(2,6-difluorophenyl)-2-(methyloxy)-7-oxo-5,6,7,8-tetrahydropyrimido-[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide, (0.027 g, 0.05 mmol) was dissolved in methanol (5 mL) and treated in portions with 60% NaH in mineral oil (0.1g, 2.5 mmol) while stirring under argon at room temperature. The mixture was stirred for 30 minutes. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with 0-3% MeOH / CH_2Cl_2 to give the title compound as a white solid. mp (dec) 225-228 °C; LC-MS *m/z* 508 $(M+H)^+$, 2.04 min (ret. time).

Example 11

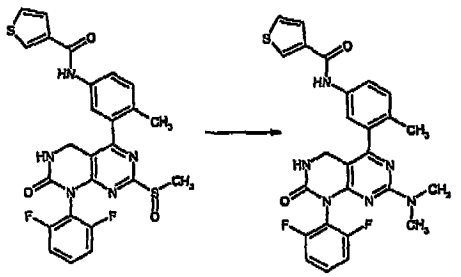
N-{3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide, (0.027 g, 0.05 mmol) was dissolved in DMF (4 mL) and 4-aminopiperidine (0.1 g, 1.0 mmol) was added. The mixture was stirred under argon at room temperature for 17 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with CH_2Cl_2 followed by 6 : 0.25 : 0.025, CH_2Cl_2 : isopropanol : NH_4OH and then by 6 : 0.5 : 0.025 CH_2Cl_2, : isopropanol : NH_4OH to give the title compound as a white amorphous solid. This was crystallized from CH_2Cl_2/hexane to give the title compound as a white crystalline solid. mp (dec) 250-261 °C; LC-MS *m/z* 576 $(M+H)^+$, 1.6 min (ret. time).

Example 12

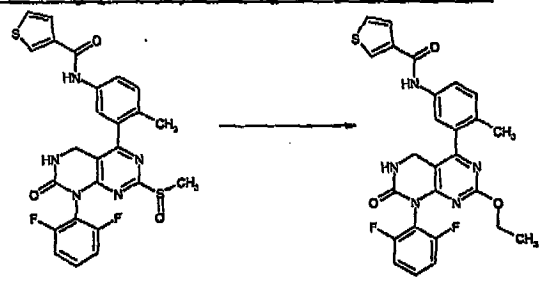
N-{3-[8-(2,6-difluorophenyl)-2-(dimethylamino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide



The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide, (0.054 g, 0.1 mmol) was dissolved in a mixture of DMF (0.5 mL) and CH_2Cl_2 (10 mL), and 40% dimethylamine in water (1 mL) was added. The mixture was stirred under argon at room temperature for 3 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with 10-60% EtOAc/CH_2Cl_2 to give the title compound as a white amorphous solid. The solid was crystallized from CH_2Cl_2 / hexane to give the title compound as a white crystalline solid. mp 214-215 °C; LC-MS *m/z* 521 $(M+H)^+$, 2.0 min (ret. time).

Example 13

N-{3-[8-(2,6-difluorophenyl)-2-(ethyloxy)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide

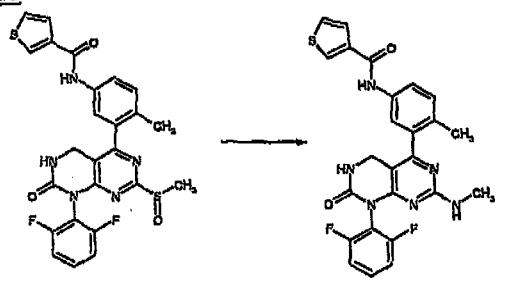


The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide, (0.054 g, 0.1 mmol) was dissolved in ethanol (5 mL) and treated in portions with 95% NaH (0.1g, 4 mmol) while stirring under argon at room temperature. The mixture was stirred under argon at room temperature for 1 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with 0-3% MeOH / CH_2Cl_2 to give the title compound as a white amorphous solid. This solid was crystallized from CH_2Cl_2 / hexane to give the title compound as a white crystalline solid. mp (dec) 199-202 °C; LC-MS *m/z* 522 $(M+H)^+$, 2.15 min (ret. time).

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Example 14

N-{3-[8-(2,6-difluorophenyl)-2-(methylamino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide

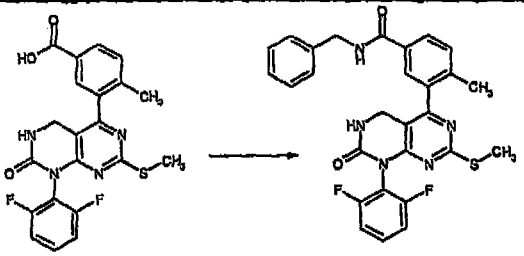


The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-thiophenecarboxamide, (0.054 g, 0.1 mmol) was dissolved in THF (20 mL) and a 2M solution of methylamine in THF (1 mL) was added. The mixture was stirred at room temperature for 4 days. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (10 g) eluted with 0-10% MeOH / CH_2Cl_2 to give the title compound as an off-white amorphous solid. mp (dec) 203-207°C; LC-MS *m/z* 507 $(M+H)^+$, 1.76 min (ret. time).

Example 15

3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

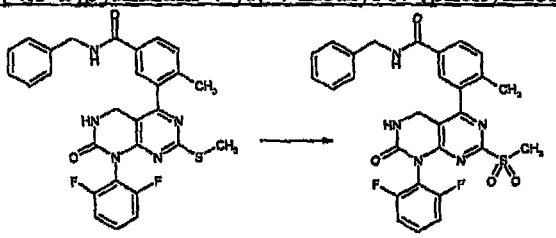
15a) 3-[8-(2,6-Difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide



The compound 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylbenzoic acid (0.597 g, 1.35 mmol), benzyl amine (0.445 mL, 4.0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.311 g, 1.62 mmol), 1-hydroxybenzotriazole hydrate (0.219 g, 1.62 mmol), were dissolved in CH_2Cl_2 (50 mL) and stirred under

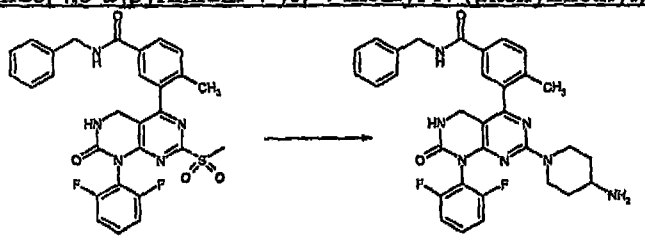
argon at room temperature for 16 h. The solvent was pumped off *in vacuo*. The reaction mixture was partitioned between ethyl acetate and water. The organic phase washed 3X with water, 1X brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was flash chromatographed on silica gel (25 g) eluted with a gradient of 6 : 1 : 0.1, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound. Crystallization from CH_2Cl_2 / hexane gave the title compound as a white crystalline solid. m.p. (dec)154-159 °C; LC-MS *m/z* 532 $(M+H)^+$, 2.24 min (ret. time).

15b) 3-[8-(2,6-Difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide



The compound 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.41 g, 0.77 mmol) was dissolved in CH_2Cl_2 (25 mL). 3-Chloroperoxybenzoic acid (50-60%) (0.505 g, ~1.62 mmol) was added and the mixture stirred for 16 h at room temperature. The solvent was pumped off *in vacuo* and the residue partitioned between EtOAc and water. The organic phase washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product was flash chromatographed on silica gel eluted with 0-5% MeOH / CH_2Cl_2 to give the title compound. Crystallization from CH_2Cl_2 /hexane to give the title compound as a white crystalline solid. m.p. 239-241 °C; LC-MS *m/z* 564 $(M+H)^+$, 2.01 min (ret. time).

15c) 3-[2-(4-Amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

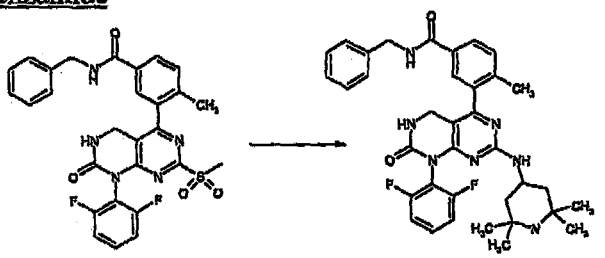


The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide,

(0.056g, 0.1 mmol) was dissolved in THF (5 mL) and 4-aminopiperidine (0.2 g, 2.0 mmol) was added. The mixture was stirred under argon at room temperature for 17 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (15 g) eluted with 6 : 1 : 0.1, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound as a white amorphous solid. m.p. (dec) 210-266 °C; LC-MS *m/z* 584 $(M+H)^+$, 1.68 min (ret. time).

Example 16

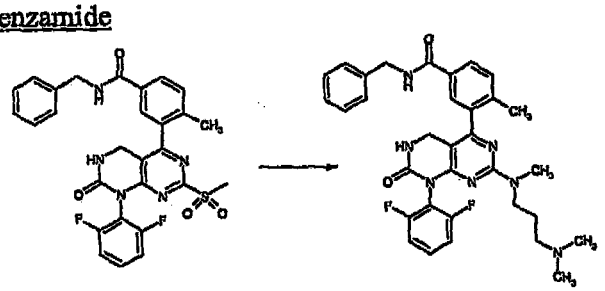
3-{8-(2,6-Difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide



The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.056g, 0.1 mmol) was dissolved in THF (5 mL) and 4-amino-2,2,6,6-tetramethylpiperidine (0.032 g, 0.2 mmol) was added. The mixture was stirred under argon at room temperature for 17 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (15 g) eluted with 6 : 0.5 : 0.05, to 6 : 1 : 0.1, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound as a white amorphous solid. mp (dec) 160-165°C; LC-MS *m/z* 640 $(M+H)^+$, 1.62 min (ret. time).

Example 17

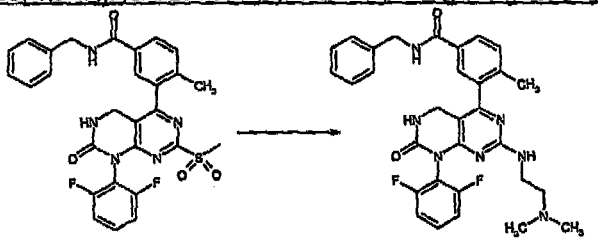
3-{8-(2,6-Difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide



The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.050g, 0.089 mmol) was dissolved in THF (5 mL) and N,N,N'-trimethyl-1,3-propanediamine (0.054 g, 0.44 mmol) was added. The mixture was stirred under argon at room temperature for 3 h. The reaction was not complete, so additional N,N,N'-trimethyl-1,3-propanediamine (0.108 g, 0.88 mmol) was added and the mixture stirred at room temperature for an additional 17 h, followed by heating to 40° C for 1 h. The solvents were pumped off *in vacuo*. The residue was taken up in EtOAc washed with 1M NaOH (2x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 6 : 1 : 0.05, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound as a white amorphous solid. mp 124-127 °C; LC-MS *m/z* 600 $(M+H)^+$, 1.84 min (ret. time).

Example 18

3-(8-(2,6-Difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide

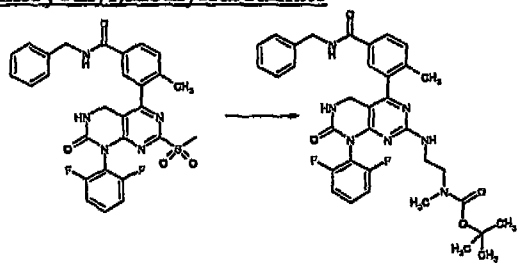


The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.050g, 0.089 mmol) was dissolved in THF (5 mL) and N,N-dimethylethylenediamine (0.2 g, 2.2 mmol) was added. The mixture was stirred under argon at room temperature for 4 h. The solvents were pumped off *in vacuo*. The residue was taken up in EtOAc washed with 1M NaOH (2x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 6 : 1 : 0.05, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound as a white amorphous solid. mp 148-150 °C; LC-MS *m/z* 572 $(M+H)^+$, 1.68 min (ret. time).

Example 19

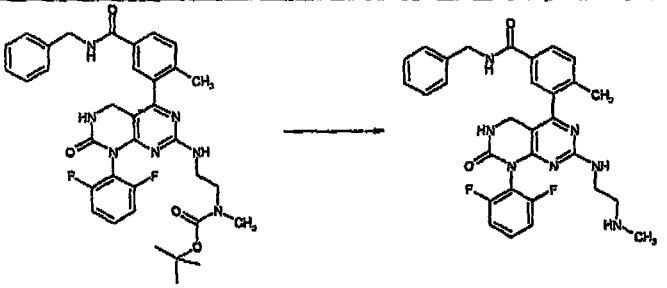
3-(8-(2,6-Difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide

19a) 1,1-Dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(phenylmethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate



The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.065g, 0.115 mmol) was dissolved in THF (5 mL) and 1,1-dimethylethyl (2-aminoethyl)methylcarbamate (0.082 g, 0.46 mmol) was added. The mixture was stirred under argon at room temperature for 16 h. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (20 g) eluted with 0-50% EtOAc / CH_2Cl_2. This material was dissolved in CH_2Cl_2 and the title compound was precipitated as a white amorphous solid. mp 160-163 °C; LC-MS *m/z* 658 $(M+H)^+$, 2.07 min (ret. time).

19b) 3-(8-(2,6-Difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide

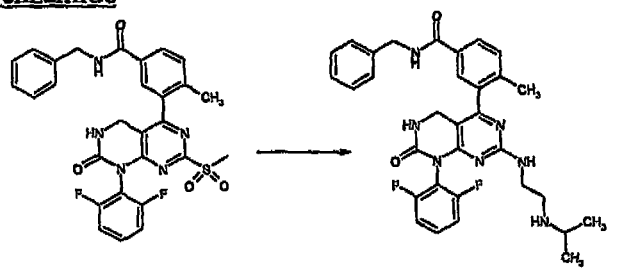


The compound 1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(phenylmethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate, (0.036 g, 0.055 mmol) was dissolved in CH_2Cl_2 (4 mL) and stirred under argon at 0 °C. Trifluoroacetic acid (1 mL) was added and the mixture stirred under argon at 0°C for 2 h. The solvents were pumped off *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The mixture was made basic by the addition of 1M NaOH. The organic phase was washed with H_2O (2x), with brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was flash chromatographed on silica gel (10 g) eluted with

6 : 1 : 0.05, CH_2Cl_2 : isopropanol : NH_4OH to give the title compound as a white amorphous solid. mp 157-161 °C; LC-MS *m/z* 558 $(M+H)^+$, 1.49 min (ret. time).

Example 20

3-[8-(2,6-Difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

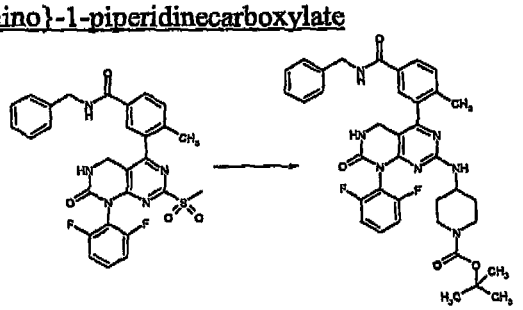


The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.060g, 0.106 mmol) was dissolved in THF (5 mL) and N-isopropylethylenediamine (0.1 g, 0.98 mmol) was added. The mixture was stirred under argon at room temperature for 3 h. The solvents were pumped off *in vacuo*. The residue was taken up in EtOAc washed with 1M NaOH (1x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated The residue was flash chromatographed on silica gel (10 g) eluted with 6 : 0.5 : 0.05, CH_2Cl_2 : ethanol : NH_4OH to give the title compound as a off-white amorphous solid. mp 133-137 °C; LC-MS *m/z* 586 $(M+H)^+$, 1.5 min (ret. time).

Example 21

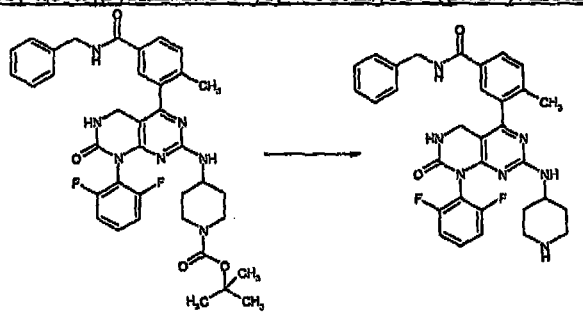
3-[8-(2,6-Difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide

21a) 1,1-Dimethylethyl 4-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(phenylmethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate



The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.08g, 0.14 mmol) was dissolved in CH_2Cl_2 (5 mL) and 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (0.0365 g, 0.175 mmol) and triethylamine (0.0284 g, 0.28 mmol) were added. The mixture was stirred under argon at room temperature overnight with only minor product formation. The reaction mixture was then heated to reflux for 24 h. The reaction still was not complete, so additional 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (0.146 g, 0 7 mmol) was added and the mixture stirred at reflux for 5 days. The solvents were pumped off *in vacuo*. The residue was taken up in EtOAc washed with 1M NaOH (2x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated The residue was flash chromatographed on silica gel (20 g) eluted with 0-50% EtOAc / CH_2Cl_2 to give the title compound as a white amorphous solid. mp (dec) 167-172 °C; LC-MS *m/z* 684 $(M+H)^+$, 2.13 min (ret. time).

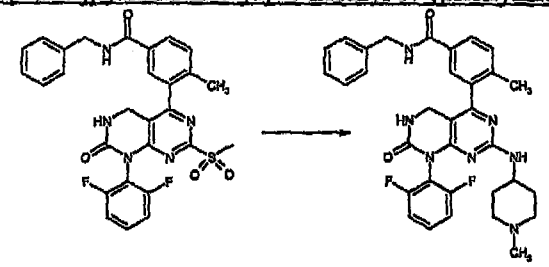
21b) 3-[8-(2,6-Difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide



The compound 1,1-dimethylethyl 4-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(phenylmethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate, (0.052 g, 0.076 mmol) was dissolved in CH_2Cl_2 (4 mL) and stirred under argon at 0 °C. Trifluoroacetic acid (1 mL) was added and the mixture stirred under argon at 0 °C for 2 h. The solvents were pumped off *in vacuo*, and the residue was partitioned between EtOAc and H_2O. The mixture was made basic by the addition of 1 M NaOH. The organic phase was washed with H_2O (2x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was flash chromatographed on silica gel (10 g) eluted with 6 : 2 : 0.2, CH_2Cl_2 : ethanol : NH_4OH to give the title compound as a white amorphous solid. mp (dec) 172-176 °C; LC-MS *m/z* 584 $(M+H)^+$, 1.49 min (ret time).

Example 22

3-{8-(2,6-Difluorophenyl)-2-[(1-methyl-4-piperidinyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(phenylmethyl)benzamide

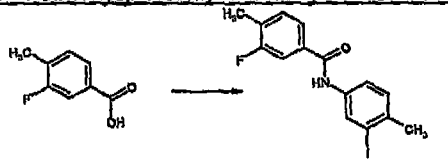


The compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide, (0.06g, 0.106 mmol) was dissolved in CH_2Cl_2 (5 mL) and 4-amino-1-methylpiperidine (0.031 g, 0.265 mmol) was added. The mixture was stirred under argon at room temperature for 16 h with some product formation. The reaction was not complete, so additional 4-amino-1-methylpiperidine (0.031 g, 0.265 mmol) was added and the mixture stirred for an additional 24 h. The reaction still was not complete, and was then heated to reflux for 24 h. The solvents were pumped off *in vacuo*. The residue was taken up in EtOAc washed with 1M NaOH (2x), brine (1x), dried over anhydrous Na_2SO_4, filtered and evaporated The residue was flash chromatographed on silica gel (20 g) eluted with 6 : 2 : 0.2, CH_2Cl_2 : ethanol : NH_4OH to give the title compound as a white amorphous solid. mp (dec) 152-154°C; LC-MS *m/z* 598 $(M+H)^+$, 1.62 min (ret. time).

Example 23

N-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-fluoro-4-methylbenzamide

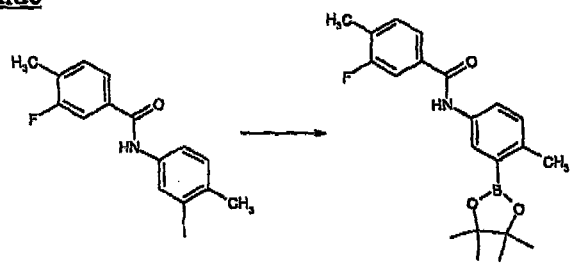
23a) 3-Fluoro-N-(3-iodo-4-methylphenyl)-4-methylbenzamide



A stirred suspension of 3-fluoro-4-methyl benzoic acid (1.15g, 7.44 mmol) in CH_2Cl_2 (50 mL) and DMF (2 drops) was cooled to 0 °C under argon and treated with oxalyl chloride (0.71 mL, 8.18 mmol) dropwise. The mixture was warmed to r.t. and stirred for 1 h. In a separate flask, 3-iodo-4-methyl aniline (2.60g, 11.16mmol), K_2CO_3 (1.54g, 8.93 mmol) and pyridine (4 drops) were suspended in CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C under argon and the acid chloride

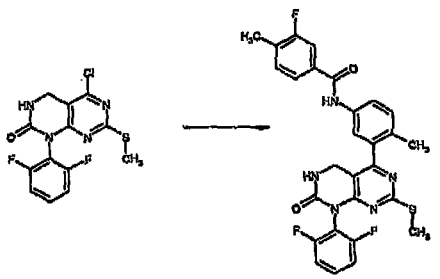
reaction mixture was slowly added. Upon complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 3 days. The resultant solid was filtered off and the reaction mixture was diluted with EtOAc. The organic phase was washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Diethyl ether was added and the impurities were filtered off, affording the title compound as a brown solid. ^{1}H-NMR (400 MHz, d_6-DMSO) δ: 10.24 (1H, s), 8.32 (1H, d), 7.77 (3H, m), 7.46 (1H, t), 7.32 (1H, t), 2.35 (3H, s), 2.32 (3H, s).

23b) Fluoro-4-methyl-N-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzamide



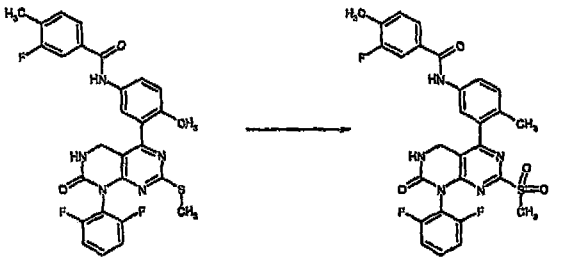
The compound 3-fluoro-N-(3-iodo-4-methylphenyl)-4-methylbenzamide (1.10g, 2.98 mmol), bis(pinacolato)diboron (1.51g, 5.96 mmol) and potassium acetate (0.90g, 9.24 mmol) were suspended in DMF (50 mL) and heated to 80 °C under argon. The reaction mixture was degassed with argon for 5 minutes at this temperature and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.109 g, 5 mol %) was added. The reaction was maintained at 80 °C for 17 h. Silica gel (15g) was added and the DMF removed *in vacuo*. The dry silica gel was added to the top of a flash chromatography column and eluted with EtOAc/hexane (1:9) to yield a white solid which was recrystallised from hexane to afford the title compound as a white solid. LC-MS *m/z* 370 $(M+H)^+$, 2.59 min (ret. time).

23c) N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide



The compound fluoro-4-methyl-N-[4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]benzamide (0.323 g, 0.875 mmol) and 5-chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (0.2 g, 0.583 mmol) were dissolved in 1,4-dioxane (5 mL) and potassium carbonate (0.322 g, 2.332 mmol) and water (1.2 mL) were added. The mixture was degassed with argon for 10 min. and tetrakis(triphenylphosphine)palladium(0) (0.034 g, 5 mol %) was added. The mixture was heated to 95 °C and maintained at this temperature for 17 h. Most of the dioxane was removed *in vacuo* and the residue diluted with CH_2Cl_2. The organic phase was washed with water, brine twice, dried over Na_2SO_4, filtered and evaporated to yield the crude residue. Purification was accomplished by flash chromatography on silica gel, eluting with a CH_2Cl_2 - 2% MeOH / CH_2Cl_2 gradient. The resultant product was triturated with cold diethyl ether to afford the title compound as a white solid. mp 167-173 °C; LC-MS *m/z* 550 $(M+H)^+$, 2.37 min (ret. time).

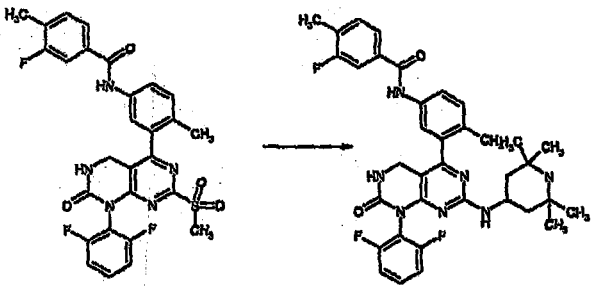
23d) *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide



The compound N-{3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide, (0.188 g, 0.343 mmol) was suspended in CH_2Cl_2 (5 mL) and DMF (1 mL) and treated with 3-chloroperoxybenzoic acid (50-60%) (0.192 g, 1.133 mmol) under argon. The reaction was stirred at room temperature for 4 h before the solvent was evaporated. The resultant solid was triturated with diethyl ether, filtered, and washed with ether to yield the title compound as a white solid. mp >270 °C; LC-MS *m/z* 582 $(M+H)^+$, 2.12 min (ret. time).

23e) *N*-(3-{8-(2,6-difluorophenyl)-7-oxo-2-[(2,2,6,6-tetramethyl-4-piperidinyl)amino]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-fluoro-4-methylbenzamide

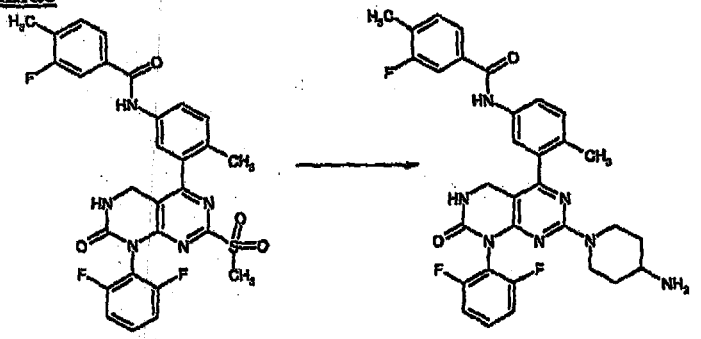
155



The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide (0.070 g, 0.107 mmol) was dissolved in DMF (1.5 mL) and treated with 4-amino-2,2,6,6-tetramethylpiperidine (62 ul, 0.361 mmol). Stirring at room temperature and heating to 70 °C under argon produced no reaction so the mixture was microwaved at 200 °C for 15 min. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel, eluting with CH_2C_2 - 10% MeOH / CH_2C_2. The product was repurified by the same method to afford the title compound as a white solid. mp (dec) 220 °C; LC-MS *m/z* 659 $(M+H)^+$, 1.94 min (ret. time).

Example 24

N-{3-[2-(4-amino-1-piperidinyl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide

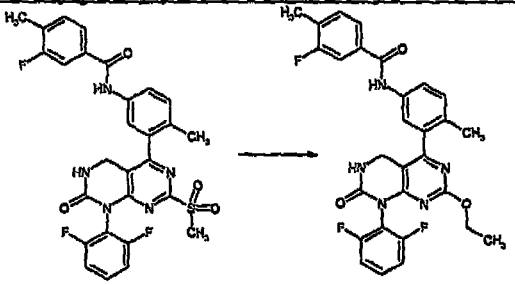


The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide (0.080 g, 0.137 mmol) and 4-aminopiperidine (0.055 g, 0.551 mmol) were suspended in THF (3 mL) and stirred under argon for 3 days. The completed reaction mixture was diluted with EtOAc and the organic phase washed with water, brine (twice), dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel, eluting with 6 : 0.5 :

0.05 CH_2Cl_2 : EtOH : NH_4OH to afford the title compound as an off-white solid. mp 240 °C; LC-MS *m/z* 602 $(M+H)^+$, 1.79 min (ret. time).

Example 25

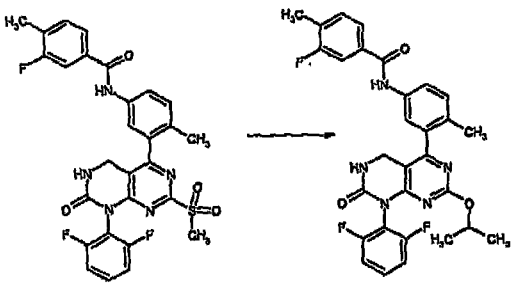
N-{3-[8-(2,6-difluorophenyl)-2-(ethyloxy)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide



Dry ethanol (2 mL) was treated with NaH (0.0056 mg, 0.140 mmol, 60% in mineral oil) under argon and stirred for 10 min.. The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide (0.064 g, 0.110 mmol) was added in ethanol (2 mL). The reaction was stirred under argon for 1 h and then warmed to 70 °C for 2 h. The reaction mixture was diluted with EtOAc and the organics washed with water, brine (twice), dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by flash chromatography on silica gel, eluting with a CH_2Cl_2 - 10% EtOAc / CH_2Cl_2 gradient to afford the title compound as a white solid. mp 257.3-262.5 °C; LC-MS *m/z* 548 $(M+H)^+$, 2.37 min (ret. time).

Example 26

N-(3-{8-(2,6-difluorophenyl)-2-[(1-methylethyl)oxyl-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methylphenyl)-3-fluoro-4-methylbenzamide



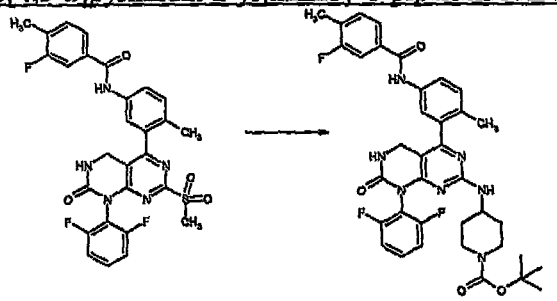
Dry *iso*-propanol (2 mL) was treated with NaH (0.00612 g, 0.153 mmol, 60% in mineral oil) under argon and stirred for 10 min. The product of Example 23d, *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-

tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide (0.070 g, 0.120 mmol) was added in *iso*-propanol (2 mL). The reaction was stirred under argon for 1 hour and then warmed to 80 °C for 3 hours. The reaction mixture was diluted with EtOAc and the organics washed with water, brine (twice), dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by flash chromatography on silica gel, eluting with a CH_2Cl_2 - 10% EtOAc / CH_2Cl_2 gradient to afford the title compound as a white solid. mp 253.5-255.4 °C; LC-MS *m/z* 562 $(M+H)^+$, 2.44 min (ret. time).

Example 27

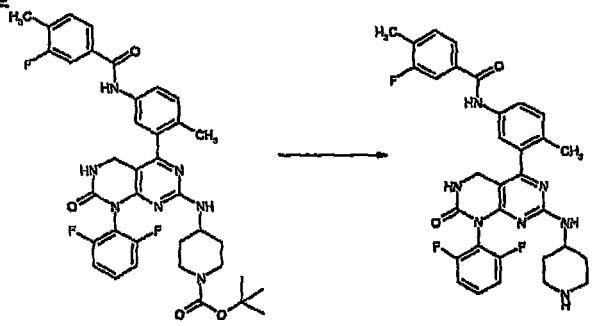
N-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide

27a) 1,1-dimethylethyl 4-{[8-(2,6-difluorophenyl)-4-(5-{[(3-fluoro-4-methylphenyl)carbonyl]amino}-2-methylphenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}-1-piperidinecarboxylate



The compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide, (0.1 g, 0.172 mmol), 1,1-dimethylethyl 4-amino-1-piperidinecarboxylate (0.11 g, 0.549 mmol) and triethylamine (0.5 mL) were suspended in stirred THF (4 mL) and heated to 60 °C under argon for 4 days. Dioxane (4 mL) was added and the reaction warmed to 85 °C for 2 days and then 95 °C for 1 day. The reaction mixture was diluted with EtOAc and the organics were washed with water, brine (twice), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel, eluting with 10% EtOAc / CH_2Cl_2 - 50% EtOAc / CH_2Cl_2 to afford the title compound as a white solid. LC-MS *m/z* 702 (M+H)+, 2.41 min (ret. time)

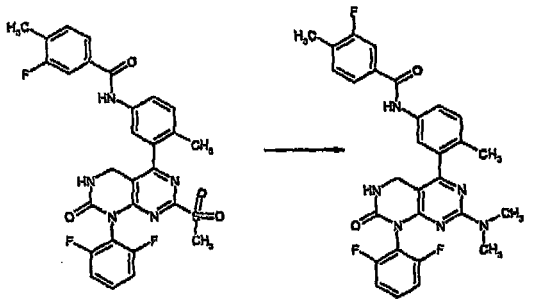
27b) *N*-{3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-piperidinylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide



The product of Example 27a (0.07 g, 0.1 mmol) was suspended in CH_2Cl_2 (3 mL) and treated with TFA (2 mL) on ice under argon. The reaction mixture was stirred at 0 °C for 90 min before most of the solvent and TFA were removed *in vacuo*. The crude residue was basified with NaOH (1M) and extracted with EtOAc. The organics were washed with water, brine (twice), dried over Na_2SO_4, filtered and evaporated. The crude residue was purified by flash chromatography on silica gel, eluting with 6 : 0.5 : 0.025 CH_2Cl_2 : EtOH : NH_4OH and then by prep HPLC to afford the title compound as a white solid. mp 218-223.5 °C; LC-MS *m/z* 602 $(M+H)^+$, 1.84 min (ret. time).

Example 28

N-{3-[8-(2,6-difluorophenyl)-2-(dimethylamino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide



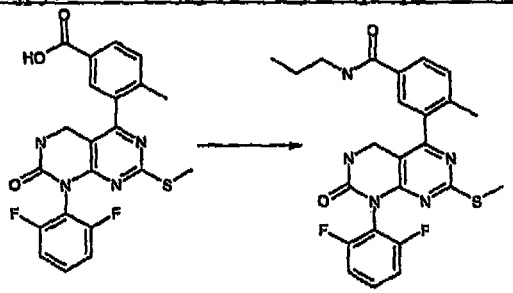
To the compound *N*-{3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methylphenyl}-3-fluoro-4-methylbenzamide (0.075 g, 0.129 mmol) in THF (4 mL) was added a 1.0 M solution of dimethylamine in THF (0.322 mL, 0.322 mmol). The mixture was stirred under argon for 3 days. The completed reaction mixture was diluted with EtOAc and the organic phase washed with water, brine (2x), dried over Na_2SO_4, filtered and

concentrated. The crude residue was purified by flash chromatography on silica gel, eluting with 1% MeOH / CH_2Cl_2 to afford the title compound as a white solid. mp 257.8-264.3 °C; LC-MS *m/z* 547 $(M+H)^+$, 2.24 min (ret. time).

Example 29

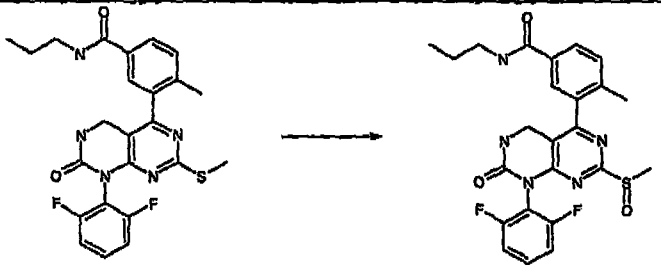
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide

29a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



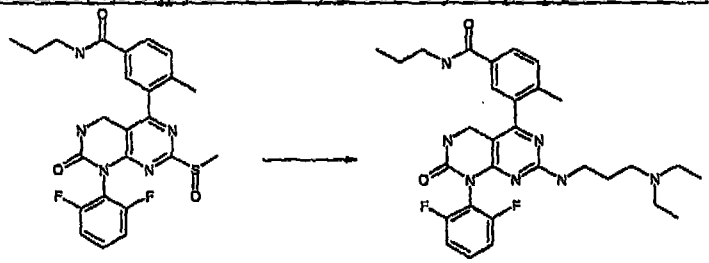
To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (1.2 g, 2.71 mmol) in CH_2Cl_2 (60 mL) was added propylamine (0.7 mL, 8.51 mmol), HATU (1.08 g, 2.84 mmol) and diisopropyl ethyl amine (1.2 mL, 6.9 mmol). The reaction mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL) and shaken. The layers were separated and the organic layer was washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (load column with DCM, mobile phase EtOAc/Hexane) then provided the title compound as a white solid 1.10 g (84 %). LC-MS m/z 484 $(M + H)^+$.

29b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (600 mg, 1.24 mmol) in CH_2Cl_2 (15 mL) was added m-CPBA (293 mg, 1.31 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. CombiFlash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 475 mg (77 %). LC-MS m/z 500 $(M + H)^+$.

29c) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (430 mg, 0.86 mmol) in CH_2Cl_2 (25 mL) was added *N,N*-diethyl-1,3-propanediamine (0.272 mL, 1.73mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM [90] + MeOH [7] + NH_4OH [3]) provided the title compound as a white solid (452 mg, 93 %). LC-MS m/z 566 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.00 (m, 9 H), 1.54 (m, 2 H), 1.65 (m, 2H), 2.30 (s, 3 H), 2.36 (m, 2 H), 2.50 (m, 4H), 3.08 (s, 2 H), 3.37 (m, 2 H), 4.11 (s, 2 H), 7.15 (m, 2 H), 7.50 (m, 2 H), 7.69 (s, 1 H), 7.85 (t, 1 H).

29d) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide

Methyl t-butyl ether (MTBE) (21.2 mL) was added to partially crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free base (0.847 g). The resulting slurry was temperature-cycled with stirring from 10-40 °C overnight. The product was filtered, washed with MTBE, and dried overnight in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 88.8% (0.753 g) of crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base with a melting onset at 179°C (determined by DSC).

29e) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide

Acetonitrile (140 mL) was added to partially crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free base (0.867 g). The resulting mixture was temperature-cycled with stirring from 10-40 °C overnight at room temperature. The product was filtered, washed with acetonitrile, and dried overnight in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 89.2% (0.773 g) of crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free base with a melting onset at 176°C (determined by DSC).

29f) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide hydrochloride salt

Acetone (451 uL) was added to the partially crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base (25.2 mg). Hydrochloric acid was added (1.1 equivalents; 1M in 1, 4-dioxane), and the resulting mixture was temperature-cycled from 0-40 °C for a minimum of 48 hours. The product was filtered and dried *in vacuo* at room temperature. Yielded 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide HCl salt with a melting onset at 259 °C (determined by DSC).

29g) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide hemi-sulfate salt

Ethanol (3.5 mL) was added to the crystalline 3-[2-{[3-(diethylamino)-propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base (229.5 mg), and the resulting mixture was heated to 50 °C. Sulfuric acid was added (1.0 equivalents; 1M in THF). The mixture was cooled to room temperature and stirred for several hours. The product was filtered, washed with ethanol, and dried in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 30.7% (82.7 mg) of 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide hemi-sulfate (2 molecules of free base, 1 molecule of H_2SO_4) salt with a melting onset at 218 °C (determined by DSC).

29h) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide fumarate salt

Acetone with 5% water (12.2 mL) was added to the crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base (0.608 g) and solid fumaric acid (1.0 equivalents; 124.8 mg). The resulting mixture was heated to 50 °C for one hour. The mixture was cooled to room temperature and stirred for 30 minutes. The product was filtered, washed with acetone with 5% water, and dried overnight in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 85.4% (0.626 g) of 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide fumarate salt. Examination by PLM showed that the batch may contain amorphous content. Acetone with 10% water (12.9 mL) was added to the fumarate salt, and the resulting mixture stirred several hours at room temperature. The product was filtered, washed with acetone with 10% water, and dried overnight in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 51.3% (0.376 g) of 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide fumarate salt with a melting onset at 192 °C (determined by DSC).

29i) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide phosphate salt

Acetone (845 uL) was added to the crystalline 3-[2-{[3-(diethylamino)propyl]-amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base (46.9 mg), and the resulting mixture was heated to 50 °C. Phosphoric acid was added (1.0 equivalents; 1M in methanol). Additional methanol (5 uL) was added to the resulting oily mixture to increase solubility slightly. The mixture was cooled to room temperature and stirred overnight. The product was filtered and dried for at least one hour in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 67.1% (36.9 mg) of partially crystalline 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide phosphate salt.

29j) 3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide ethanedisulfonate salt

Acetonitrile (450 uL) was added to the crystalline 3-[2-{[3-(diethylamino)propyl]-amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide free-base (25.0 mg), and the resulting mixture was heated to 50 °C. Ethanedisulfonic acid was added (1.1 equivalents; 1M in methanol). The mixture was cooled to room temperature and stirred several hours. The product was filtered and dried for at least one hour in a vacuum oven at 50 °C with a slow nitrogen bleed. The yield was 62.0% (20.7 mg) of 3-[2-{[3-(diethylamino)-propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide ethanedisulfonate salt hydrate with a melting onset at < 100 °C (determined by DSC).

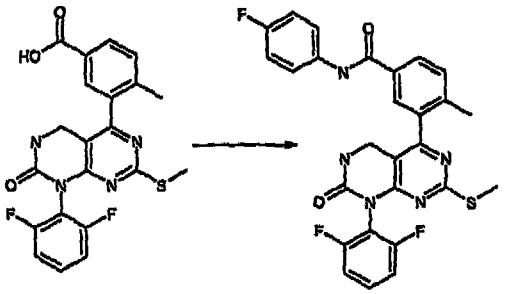
Example 30

3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

30a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

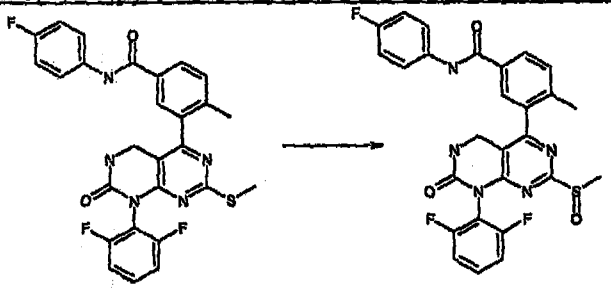
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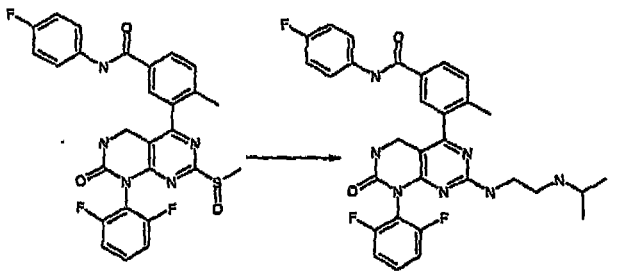
To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (2.0 g, 4.56 mmol) in CH_2Cl_2 (200 mL) were added 4-fluoroaniline (0.472 mL, 4.99 mmol), HATU (1.82 g, 4.79 mmol) and diisopropyl ethyl amine (2.0 mL, 11.5 mmol). The reaction mixture was stirred over night, diluted with CH_2Cl_2 (50 mL) and water (50 mL). The layers were separated. The organic layer was washed with brine (75 mL), collected, dried over Na_2SO_4, filtered and concentrated. Flash chromatography then provided the title compound as a white solid 2.7 g (89 %). LC-MS m/z 536 $(M + H)^+$.

30b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of the title compound from Example 30a (850 mg, 1.59mmol) in CH_2Cl_2 (50 mL) was added m-CPBA (375 mg, 1.67mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. CombiFlash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 660 mg (75 %). LC-MS m/z 552 $(M + H)^+$.

30c) 3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

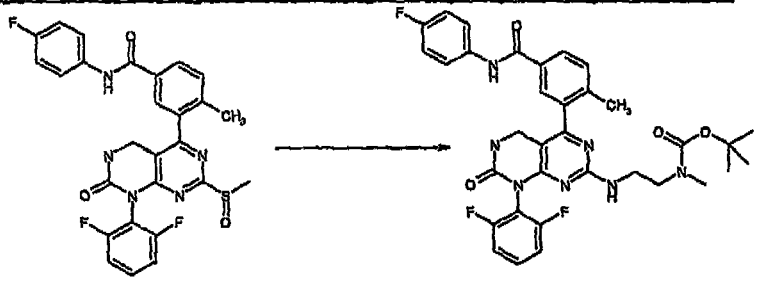


To a solution of the title compound from Example 30b (30 mg, 0.051 mmol) in THF (3 mL) and DMF (0.5 mL) were added *N*-(1-methylethyl)-1,2-ethanediamine (0.019 mL, 0.153 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (13 mg, 43 %). LC-MS m/z 588 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (d, 6 H), 2.34 (s, 3H), 2.70 (m, 3H), 3.20 (m, 2 H), 4.11 (s, 2 H), 7.10 (m, 4 H), 7.52 (m, 2 H), 7.77 (m, 2 H), 7.81 (s, 1 H), 7.97 (d, 1 H).

Example 31

3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide

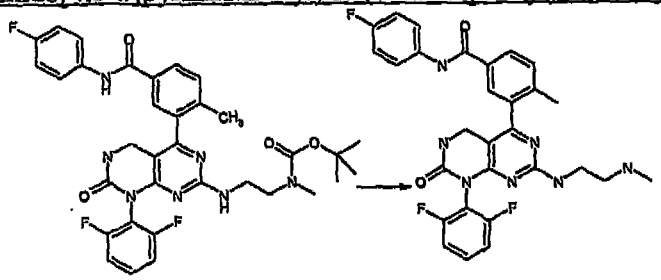
31a) 1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(5-{[(4-fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (30 mg, 0.051 mmol) in THF (3 mL) and DMF (1 mL) were added 1,1-dimethylethyl (2-aminoethyl) methylcarbamate (0.046 mL, 0.26 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (20mg, 59 %). LC-MS *m/z* 662 $(M + H)^+$.

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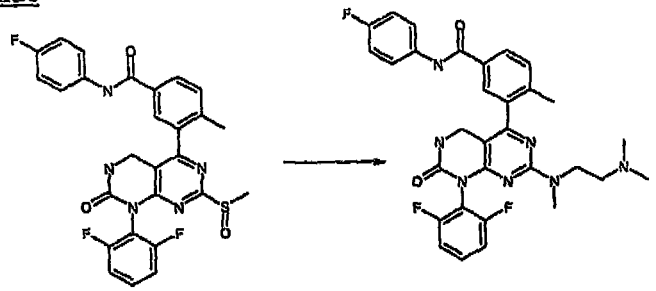
31b) 3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of 1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(5-{[(4-fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate (20 mg, 0.030 mmol) in DCM (5 mL) was added TFA (0.06 mL). The reaction mixture was stirred at room temperature overnight, quenched with triethylamine (0.2 mL) at -78^{0}C. The residue was mixed with H_2O (5.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification via a CombiFlash system (90% CH_2Cl_2 / 7% MeOH / 3% NH_4OH) then afforded the title compound (11 mg, 65%). LC-MS (ES) m/z 562 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 2.27 (s, 3H), 2.34 (s, 3H), 2.57 (m, 2H), 3.26 (m, 2H), 4.11 (s, 2H), 7.15 (m, 4H), 7.52 (m, 2H), 7.71 (m, 2H), 7.82 (s, 1H), 7.97 (d, 1H).

Example 32

3-{8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide



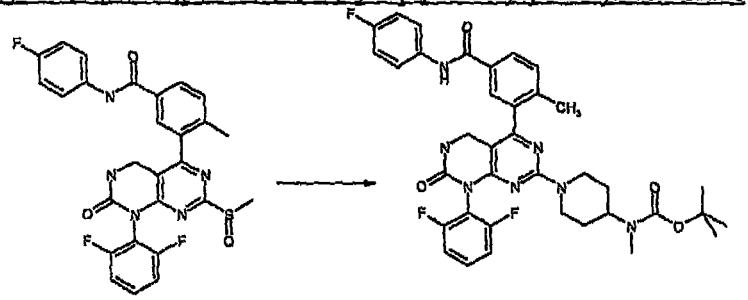
To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (40 mg, 0.073 mmol) in THF (3 mL) and DMF (0.5 mL) were added *N*,*N*,*N*'-trimethyl-1,2-ethanediamine (0.047 mL, 0.364 mmol). The resultant solution was stirred at room temperature over night. The result mixture was

concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90] +MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (11 mg, 26 %). LC-MS m/z 590 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.18 (s, 6H), 2.40 (m, 5H), 3.02 (m, 3H), 3.50 (m, 2H), 4.17 (s, 2H), 7.15 (m, 4H), 7.52 (m, 2H), 7.71 (m, 2H), 7.82 (s, 1H), 7.97 (d, 1H).

Example 33

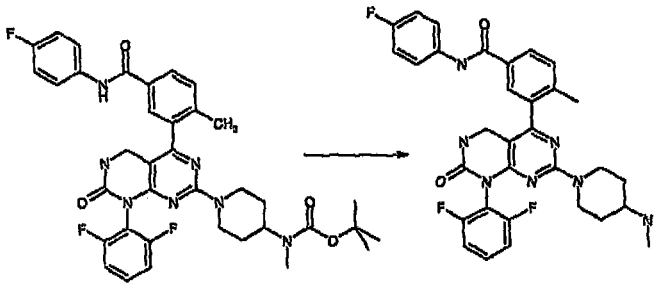
3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

33a) 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(5-{[(4-fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (40 mg, 0.073 mmol) in THF (3 mL) and DMF (0.5 mL) were added 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (49 mg, 0.229 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Flash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (12mg, 25 %). LC-MS m/z 702 $(M + H)^+$.

33b) 3-{8-(2,6-difluorophenyl)-2-[4-(methylamino)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

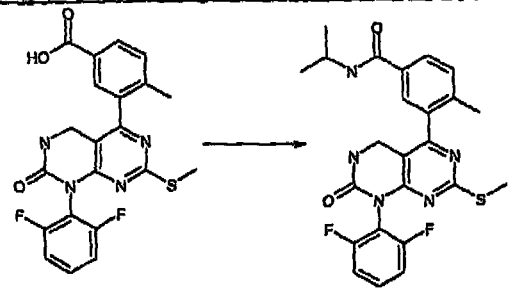


To a solution of 1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(5-{[(4-fluorophenyl)amino]carbonyl}-2-methylphenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate (12 mg, 0.017 mmol) in DCM (3 mL) was added TFA (0.04 mL). The reaction mixture was stirred at room temperature overnight, quenched with triethylamine (0.2 mL) at -78^{0}C. The residue was mixed with H_2O (5.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification via a CombiFlash system (90% CH_2Cl_2 / 7% MeOH / 3% NH_4OH) then afforded the title compound (9 mg, 87%). LC-MS (ES) m/z 602 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.18 (m, 2H), 1.81 (d, 2H), 2.34 (s, 3H), 2.37 (s, 3H), 2.58 (m, 1H), 2.78 (t, 2H), 4.11 (s, 2H), 4.40 (m, 2H), 7.15 (m, 4H), 7.52 (m, 2H), 7.70 (m, 2H), 7.82 (s, 1H), 7.98 (d, 1H).

Example 34

3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide

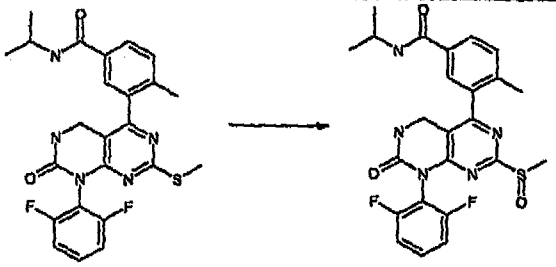
34a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (150 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) were added isopropylamine (0.087 mL, 1.02 mmol), HATU (135 mg, 0.355 mmol) and diisopropyl ethyl amine (0.2 mL, 1.15 mmol).

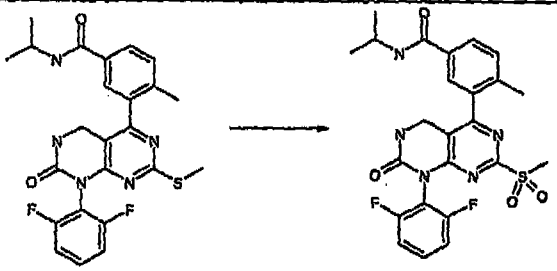
The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (50 mL) and shaked. The layers were separated and the organic layer was washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography then provided the title compound as a white solid 160 g (97 %). LC-MS m/z 484 $(M + H)^+$.

34b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



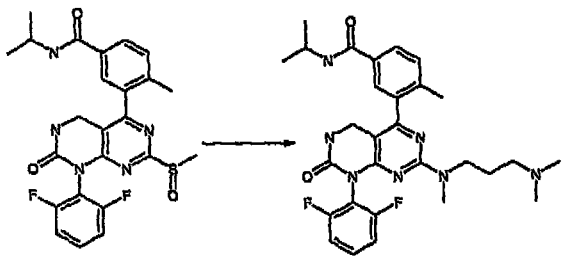
To a solution of the title compound from Example 34a (160 mg, 0.33 mmol) in CH_2Cl_2 (15 mL) was added m-CPBA (78 mg, 0.35 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. CombiFlash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 150 mg (91 %). LC-MS m/z 500 $(M + H)^+$.

34c) 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of the title compound from Example 34a (1.33 g, 2.75 mmol) in CH_2Cl_2 (130 mL) was added m-CPBA (678 mg, 3.03 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. Flash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as the minor product as a white solid 270 mg (19 %). LC-MS m/z 516 $(M + H)^+$.

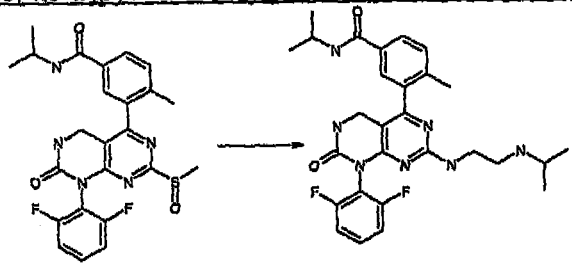
34d) 3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of the title compound from Example 34b (30 mg, 0.06 mmol) in THF (3 mL) were added *N,N,N'*-trimethyl-1,3-propanediamine (0.044 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (22 mg, 66 %). LC-MS m/z 552 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (m, 6H), 1.62 (m, 2H), 2.03 (m, 2H), 2.19 (s, 6H), 2.32 (s, 3H), 3.00 (s, 3H), 3.33 (m, 2H), 4.11 (s, 2H), 4.23 (m, 1H), 7.17 (t, 2H), 7.44 (d, 1H), 7.54 (m, 1H), 7.69 (s, 1H), 7.86 (d, 1H).

Example 35

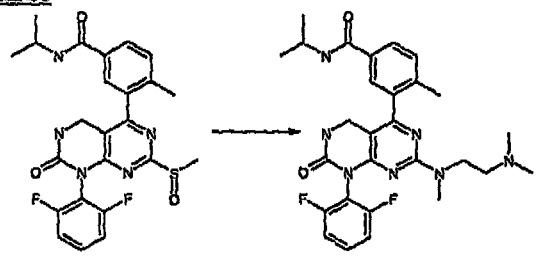
3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (30 mg, 0.06 mmol) in THF (3 mL) was added *N*-(1-methylethyl)-1,2-ethanediamine (0.019 mL, 0.15 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH [7]+NH_4OH[3]) provided the title compound as a white solid (23 mg, 71 %). LC-MS m/z 538 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (d, 3H), 1.27 (d, 3 H), 2.30 (s, 3 H), 2.58 (m, 2H), 2.70 (m, 1 H), 3.25 (m, 2 H), 4.07 (s, 2 H), 4.23 (m, 1 H), 7.16 (m, 2 H), 7.44 (d, 1 H), 7.50 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 36

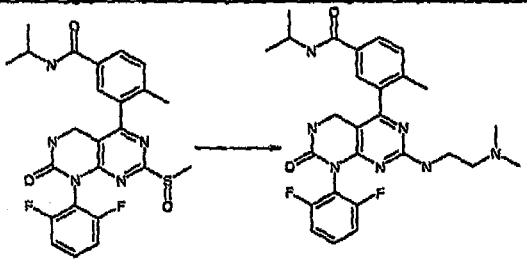
3-{8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added *N,N,N'*-trimethyl-1,2-ethanediamine (0.026 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+ MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (21 mg, 97 %). LC-MS m/z 538 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.11 (s, 6 H), 2.37 (s, 3H), 2.41 (m, 2 H), 3.02 (m, 3 H), 3.50 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 37

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide



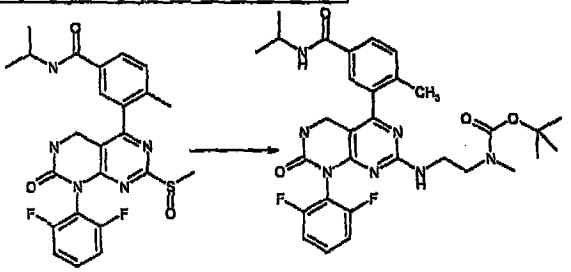
To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added *N,N*-dimethyl-1,2-ethanediamine (0.022 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH [7]+NH_4OH[3]) provided the title compound as a white solid (20 mg, 95 %). LC-MS m/z 524 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.14 (s, 6 H), 2.33 (s, 3H),

2.37 (m, 2 H), 3.22 (m, 2 H), 4.09 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 38

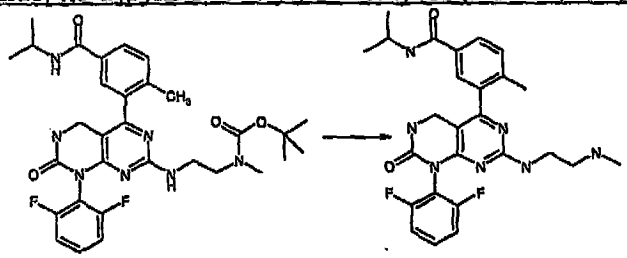
3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide

38a) 1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(1-methylethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added 1,1-dimethylethyl (2-aminoethyl) methylcarbamate (0.036 mL, 0.20 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (18mg, 74 %). LC-MS m/z 610 $(M + H)^+$.

38b) 3-(8-(2,6-difluorophenyl)-2-{[2-(methylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide

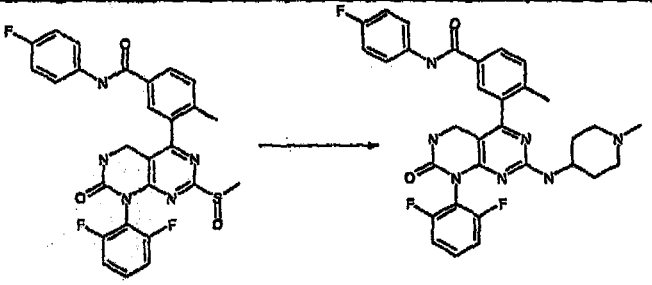


To a solution of 1,1-dimethylethyl (2-{[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(1-methylethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]amino}ethyl)methylcarbamate (18 mg, 0.030 mmol) in DCM (5

mL) was added TFA (0.05 mL). The reaction mixture was stirred at room temperature overnight, quenched with triethylamine (0.2 mL) at -78^{0}C. The residue was mixed with H_2O (5.0 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic phases were washed with saturated aq. NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification via a CombiFlash system (90% CH_2Cl_2 / 7% MeOH / 3% NH_4OH) then afforded the title compound (11 mg, 73%). LC-MS (ES) m/z 510 $(M+H)^+$; ^{1}H-NMR(MeOD) δ 1.27 (d, 6 H), 2.26 (s, 3 H), 2.30 (s, 3H), 2.56 (m, 2 H), 3.22 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 39

3-{8-(2,6-difluorophenyl)-2-[(1-methyl-4-piperidinyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

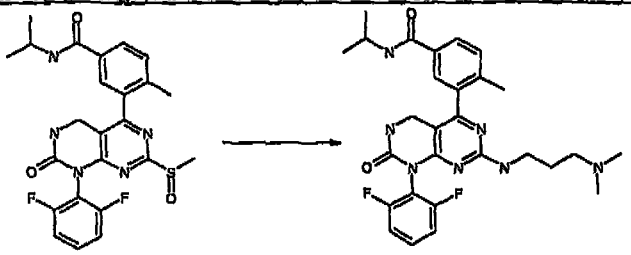


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (10 mg, 0.018 mmol) in THF (5 mL) were added 1-methyl-4-piperidinamine (10 mg, 0.088 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (9 mg, 83 %). LC-MS m/z 602 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.47 (m, 2 H), 1.84 (m, 4 H), 2.24 (s, 3 H), 2.33 (s, 3H), 2.79 (m, 2 H), 3.20 (m, 1 H), 4.13 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

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Example 40

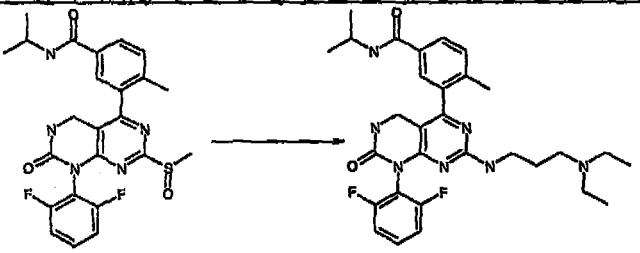
3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added *N,N*-dimethyl-1,3-propanediamine (0.023 mL, 0.18 mmol). The resultant solution was stirred at room temperature over night. The result mixture was then concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (21 mg, 97 %). LC-MS m/z 538 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.58 (m, 2 H), 2.19 (s, 6 H), 2.20 (m, 2H), 2.30 (s, 3 H), 3.15 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 41

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

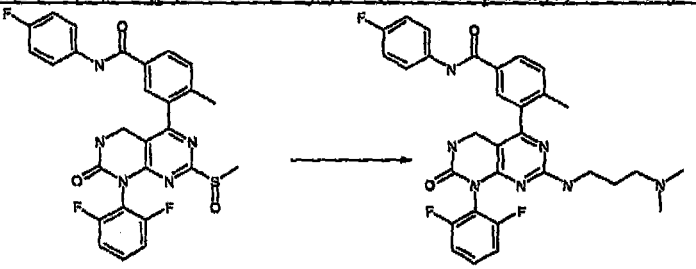


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (18 mg, 0.04 mmol) in THF (3 mL) was added *N,N*-diethyl-1,3-propanediamine (0.028 mL, 0.18 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (17 mg, 83%). LC-MS m/z 566 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 6 H), 1.27 (d, 6 H), 1.55 (m, 2 H), 2.30 (s, 3 H), 2.40 (m,

2H), 2.52 (m, 4 H), 3.07 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 42

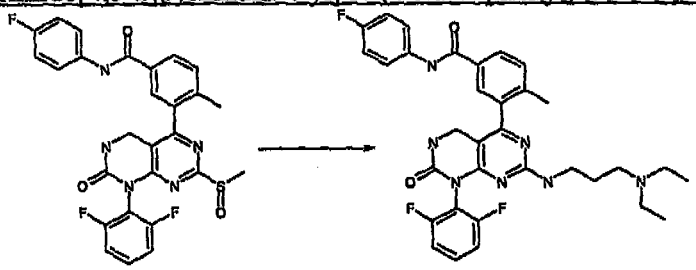
3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (10 mg, 0.018 mmol) in THF (3 mL) was added *N,N*-dimethyl-1,3-propanediamine (0.012 mL, 0.096 *mmol*). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (9 mg, 84 %). LC-MS m/z 590 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.58 (m, 2H), 2.19 (s, 6 H), 2.24 (m, 2H), 2.34 (s, 3 H), 3.10 (m, 2 H), 4.11 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 43

3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

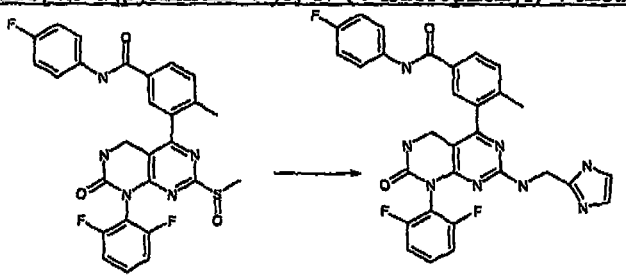


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (20 mg, 0.036 mmol) in THF (3 mL) was added *N,N*-diethyl-1,3-propanediamine (0.030 mL, 0.19 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/*DCM*[90]+MeOH[7] +NH_4OH[3]) provided the

title compound as a white solid (14 mg, 62 %). LC-MS m/z 619 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 6H), 1.55 (m, 2 H), 2.38 (s, 3H), 2.55 (m, 6 H), 3.10 (m, 2 H), 4.11 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 44

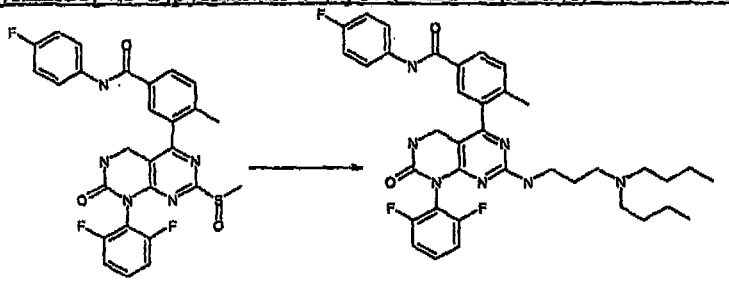
3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (20 mg, 0.036 mmol) in THF(3 mL)/ DMF(3 mL)/ DCM(3 mL) were added (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (50 mg, 0.52 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at 40^{0}C over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (7 mg, 33 %). LC-MS m/z 585 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.33 (s, 3 H), 4.13 (s, 2 H), 4.42 (s, 2 H), 6.92 (m, 2 H), 7.15 (m, 4 H), 7.50 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 45

3-[2-{[3-(dibutylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

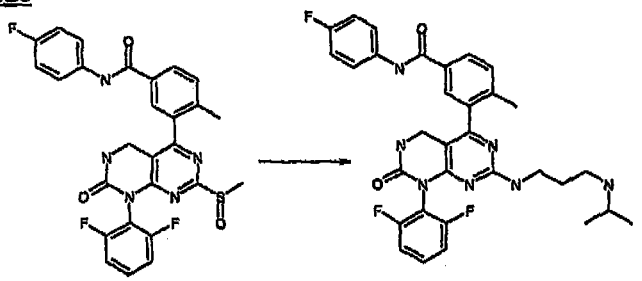


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (20 mg, 0.036 mmol) in THF(3 mL) was added *N,N*-dibutyl-1,3-propanediamine (0.041 mL, 0.182 mmol). The resultant solution was stirred at room

temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (16 mg, 66 %). LC-MS m/z 674 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 6H), 1.30 (m, 4 H), 1.40 (m, 4H), 1.50 (m, 2 H), 2.34 (s, 3H), 2.43 (m, 6 H), 3.10 (m, 2 H), 4.13 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 46

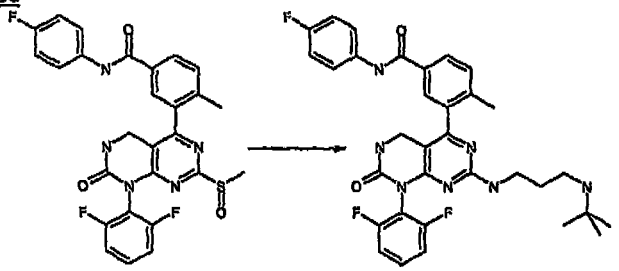
3-[8-(2,6-difluorophenyl)-2-({3-[(1-methylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (20 mg, 0.036 mmol) in THF(3 mL) was added *N*-(1-methylethyl)-1,3-propanediamine (0.025 mL, 0.179 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (14 mg, 64 %). LC-MS m/z 604 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (d, 6H), 1.65 (m, 2H), 2.34 (s, 3 H), 2.50 (m, 2H), 2.78 (m, 1 H), 3.15 (m, 2 H), 4.13 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 47

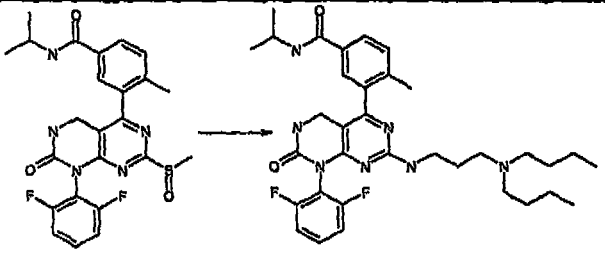
3-[8-(2,6-difluorophenyl)-2-({3-[(1,1-dimethylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (20 mg, 0.036 mmol) in THF(3 mL) was added *N*-(1,1-dimethylethyl)-1,3-propanediamine (0.028 mL, 0.177 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (18 mg, 80 %). LC-MS m/z 618 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.11 (s, 9H), 1.58 (m, 2 H), 2.34 (s, 3H), 2.48 (m, 2 H), 3.15 (m, 2 H), 4.13 (s, 2 H), 7.15 (m, 4 H), 7.53 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 48

3-[2-{[3-(dibutylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

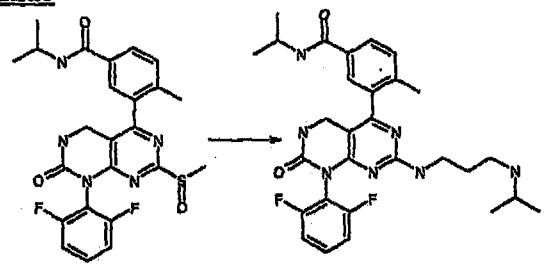


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) were added *N*,*N*-dibutyl-1,3-propanediamine (0.041 mL, 0.182 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (24 mg, 96%). LC-MS m/z 622 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 0.98 (t, 6 H), 1.30 (m, 10H), 1.46 (m, 4 H),

1.52 (m, 2 H), 2.30 (s, 3H), 2.41 (m, 6 H), 3.07 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 49

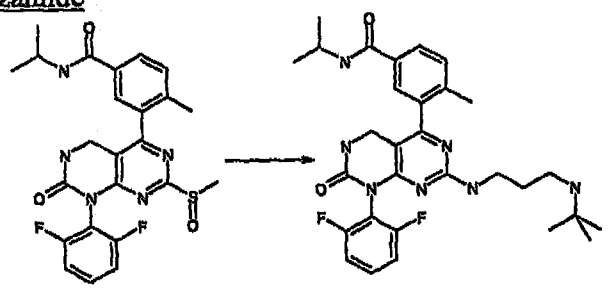
3-[8-(2,6-difluorophenyl)-2-({3-[(1-methylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added *N*-(1-methylethyl)-1,3-propanediamine (0.025 mL, 0.179 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (15 mg, 68%). LC-MS m/z 554 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (d, 6H), 1.27 (d, 6 H), 1.60 (m, 2 H), 2.31 (s, 3H), 2.50 (m, 2H), 2.75 (m, 1 H), 3.15 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 50

3-[8-(2,6-difluorophenyl)-2-({3-[(1,1-dimethylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

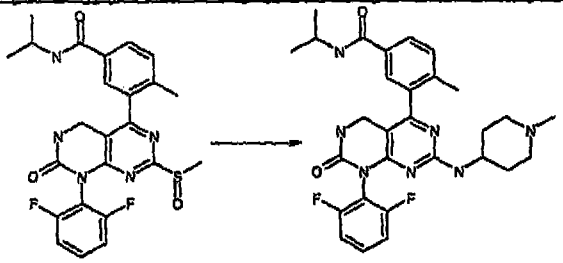


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) were added *N*-(1,1-

dimethylethyl)-1,3-propanediamine (0.028 mL, 0.177 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90] +MeOH[7] +NH_4OH[3]) provided the title compound as a white solid (17 mg, 75%). LC-MS m/z 566 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.11 (s, 9H), 1.27 (d, 6 H), 1.60 (m, 2 H), 2.31 (s, 3H), 2.45 (m, 2 H), 3.15 (m, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 51

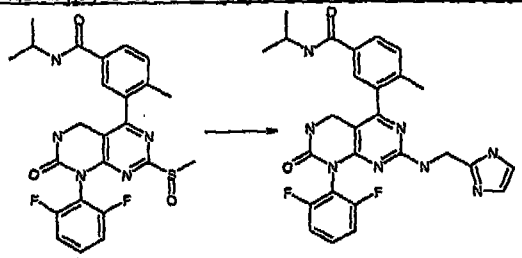
3-{8-(2,6-difluorophenyl)-2-[(1-methyl-4-piperidinyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) was added 1-methyl-4-piperidinamine (20 mg, 0.176 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (18 mg, 82%). LC-MS m/z 550 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.26 (d, 6H), 1.48 (m, 2 H), 1.88 (m, 4 H), 2.24 (s, 3 H), 2.29 (s, 3H), 2.75 (m, 2 H), 3.18 (m, 1 H), 4.09 (s, 2 H), 4.23 (m, 1 H), 7.15 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 52

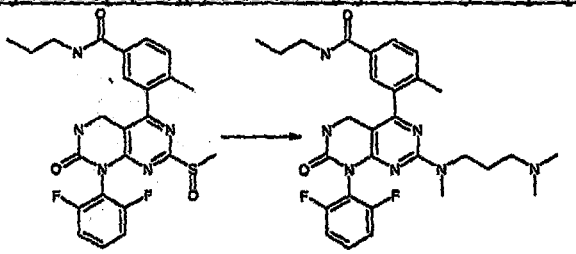
3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in THF (3 mL) were added (1*H*-imidazol-2-ylmethyl)amine dihydrochloride (50 mg, 0.52 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.574 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (7 mg, 33%). LC-MS m/z 533 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.26 (d, 6H), 2.26 (s, 3H), 4.12 (s, 2 H), 4.23 (m, 1 H), 4.36 (s, 2 H), 6.88 (s, 2 H), 7.10 (t, 2 H), 7.48 (m, 2 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 53

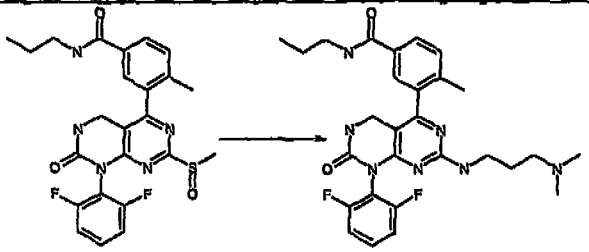
3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (20 mg, 0.04 mmol) in DCM (5 mL) was added *N,N,N'*-trimethyl-1,3-propanediamine (0.029 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (16 mg, 72%). LC-MS m/z 552 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3H), 1.66 (m, 4H), 2.03 (m, 2H), 2.19 (s, 6H), 2.32 (s, 3H), 2.98 (s, 3 H), 3.37 (m, 4 H), 4.15 (s, 2 H), 7.17 (t, 2 H), 7.45 (d, 1 H), 7.53 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 54

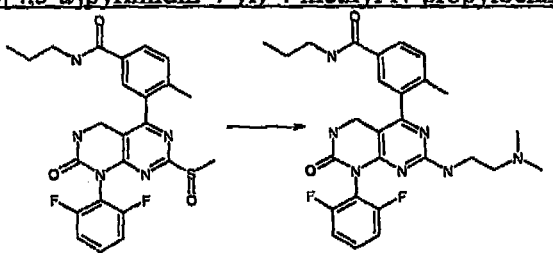
3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N,N* -dimethyl-1,3-propanediamine (0.036 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (25 mg, 77%). LC-MS m/z 552 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3H), 1.58 (m, 2H), 1.66 (m, 2H), 2.16 (m, 2H), 2.18 (s, 6H), 2.30 (s, 3H), 3.06 (m, 2 H), 3.37 (m, 2 H), 4.10 (s, 2 H), 7.17 (t, 2 H), 7.45 (d, 1 H), 7.53 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 55

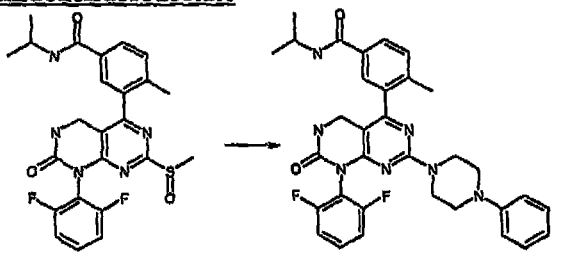
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N,N* -dimethyl-1,3-propanediamine (0.033 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (31 mg, 98%). LC-MS m/z 524 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3H), 1.66 (m, 2H), 2.13 (s, 6H), 2.38 (s, 3H), 2.83 (m, 2 H), 3.20 (m, 2 H), 3.37 (m, 2 H), 4.11 (s, 2 H), 7.15 (t, 2 H), 7.45 (d, 1 H), 7.53 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 56

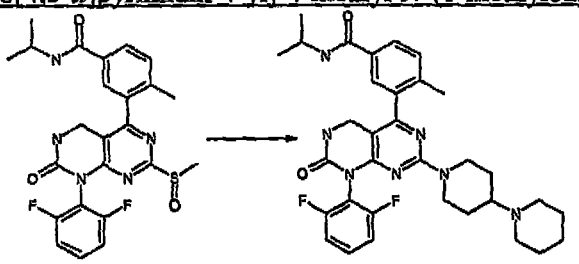
3-[8-(2,6-difluorophenyl)-7-oxo-2-(4-phenyl-1-piperazinyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamidetrifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added 1-phenylpiperazine (0.031 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA, then provided the title compound as a white solid (14 mg, 59%). LC-MS m/z 598 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6H), 2.33 (s, 3 H), 3.40 (m, 4 H), 3.87 (m, 4H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.17 (m, 2 H), 7.29 (d, 2 H), 7.44 (m, 2 H), 7.49 (m, 1 H), 7.53 (m, 1 H), 7.72 (s, 1 H), 7.87 (d, 1 H).

Example 57

3-[2-(1,4'-bipiperidin-1'-yl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

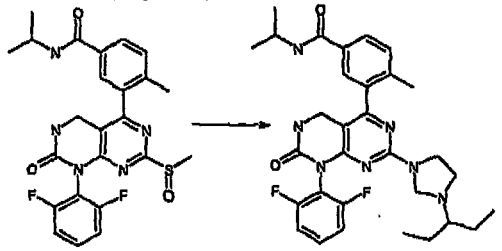


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (150 mg, 0.30 mmol) in DCM (10 mL) was added 1,4'-bipiperidine (152 mg, 0.90 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (35 mg, 19%). LC-MS m/z 604 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6H), 1.37 (m, 2 H), 1.51 (m, 2 H), 1.65 (m, 4H), 1.81

(m, 2 H), 2.33 (s, 3 H), 2.63 (m, 5 H), 2.70 (m, 2H), 4.11 (s, 2 H), 4.23 (m, 1 H), 4.50 (m, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 58

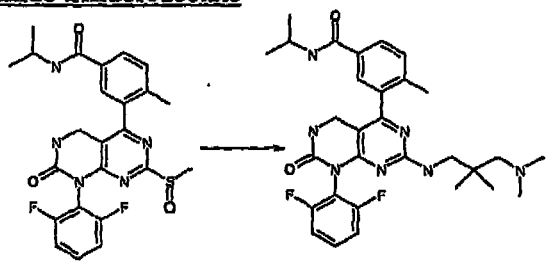
3-{8-(2,6-difluorophenyl)-2-[3-(1-ethylpropyl)-1-imidazolidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamidetrifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (30 mg, 0.06 mmol) in THF (1 mL)/$CHCl_3$ (1 mL) were added 1-(1-ethylpropyl)imidazolidine (17 mg, 0.12 mmol) and *N,N*-diisopropylethylamine (0.6 mL, 3.0 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Gilson with TFA provided the title compound as a white solid (18 mg, 52%). LC-MS m/z 578 (M + H)$^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6H), 1.32 (t, 6 H), 2.12 (m, 1H), 2.31 (s, 3 H), 2.46 (m, 1 H), 3.23 (m, 4 H), 3.50 (m, 4H), 4.09 (m, 1 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 4.50 (m, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 59

3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)-2,2-dimethylpropyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

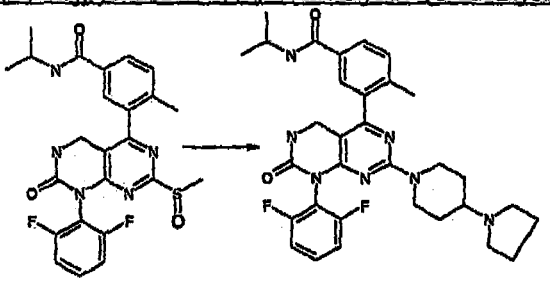


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added *N,N*,2,2-tetramethyl-1,3-propanediamine (0.032 mL, 0.20 mmol). The resultant solution was

stirred at room temperature over night. The result mixture was concentrated. Gilson with TFA provided the title compound as a white solid (5 mg, 22%). LC-MS m/z 566 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (s, 6H), 1.27 (d, 6H), 2.35 (s, 3 H), 2.67 (s, 6 H), 2.95 (m, 2 H), 3.21 (m, 2H), 4.20 (s, 2 H), 4.23 (m, 1 H), 7.18 (t, 2 H), 7.52 (m, 2 H), 7.77 (s, 1 H), 7.89 (d, 1 H).

Example 60

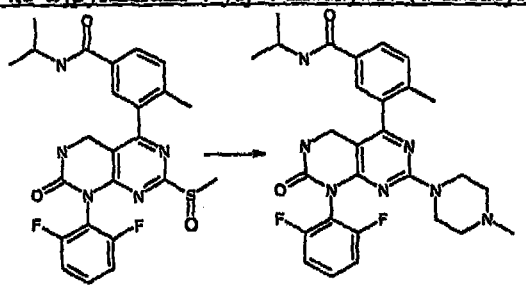
3-{8-(2,6-difluorophenyl)-7-oxo-2-[4-(1-pyrrolidinyl)-1-piperidinyl]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (80 mg, 0.16 mmol) in DCM (5 mL) was added 4-(1-pyrrolidinyl)piperidine (74 mg, 0.48 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (75 mg, 79%). LC-MS m/z 590 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6H), 1.34 (m, 2H), 1.83 (m, 4 H), 1.90 (m, 2H), 2.31 (s, 3 H), 2.40 (m, 1 H), 2.68 (m, 4 H), 2.77 (m, 2H), 4.11 (s, 2 H), 4.23 (m, 1 H), 4.44 (m, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 61

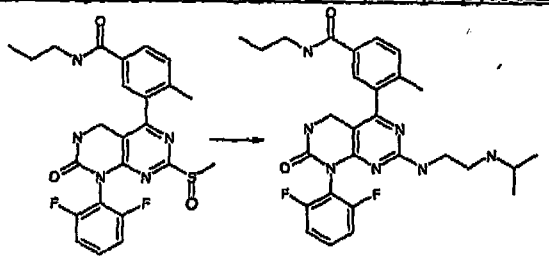
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (60 mg, 0.12 mmol) in DCM (5 mL) was added 1-methylpiperazine (0.04 mL, 0.36 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (58 mg, 90%). LC-MS m/z 536 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6H), 2.25 (s, 3 H), 2.31 (s, 3 H), 2.36 (m, 4 H), 3.57 (m, 4H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 62

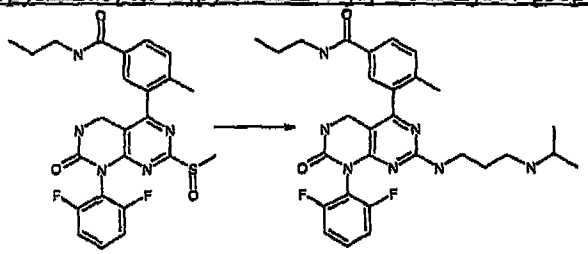
3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N*-(1-methylethyl)-1,2-ethanediamine (0.037 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (15 mg, 46%). LC-MS m/z 538 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (m, 9H), 1.65 (m, 2 H), 2.31 (s, 3H), 2.61 (m, 2 H), 2.73 (m, 2 H), 3.20 (m, 2 H), 3.40 (m, 1H), 4.11 (s, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.86 (d, 1 H).

Example 63

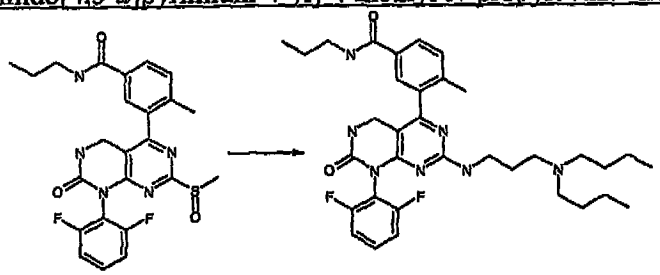
3-[8-(2,6-difluorophenyl)-2-({3-[(1-methylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N*-(1-methylethyl)-1,3-propanediamine (0.042 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (13 mg, 39%). LC-MS m/z 554 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (m, 9H), 1.65 (m, 4 H), 2.31 (s, 3H), 2.50 (m, 2 H), 2.78 (m, 2 H), 3.16 (m, 2 H), 3.43 (m, 1H), 4.11 (s, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.86 (d, 1 H).

Example 64

3-[2-{[3-(dibutylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide

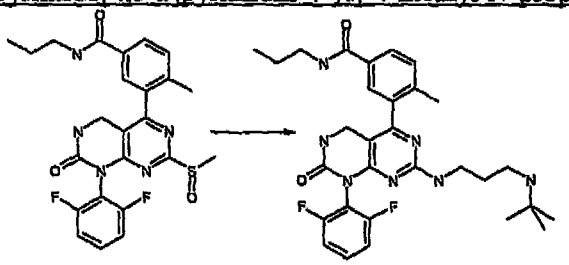


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N*,*N*-dibutyl-1,3-propanediamine (0.06 mL, 0.26 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (30 mg, 83%). LC-MS m/z 622 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (m, 10 H), 1.30 (m, 4 H), 1.50 (m, 9 H), 2.31 (s, 3H), 2.38 (m, 4 H), 2.48 (m, 2 H), 3.08

(m, 2 H), 4.11 (s, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.86 (d, 1 H).

Example 65

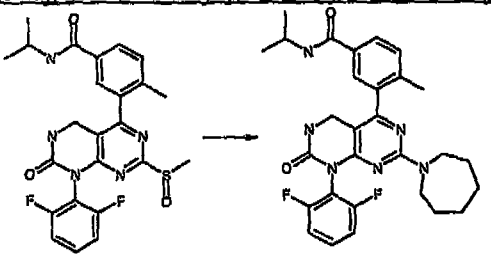
3-[8-(2,6-difluorophenyl)-2-({3-[(1,1-dimethylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (30 mg, 0.06 mmol) in DCM (5 mL) was added *N*-(1,1-dimethylethyl)-1,3-propanediamine (0.042 mL, 0.26 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (27 mg, 80%). LC-MS m/z 622 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (m, 12 H), 1.12 (m, 2 H), 1.56 (m, 2 H), 1.70 (m, 2 H), 2.31 (s, 3H), 2.48 (m, 2 H), 3.12 (m, 2 H), 4.11 (s, 2 H), 7.17 (t, 2 H), 7.46 (d, 1 H), 7.52 (m, 1 H), 7.69 (s, 1 H), 7.86 (d, 1 H).

Example 66

3-[8-(2,6-difluorophenyl)-2-(hexahydro-1*H*-azepin-1-yl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

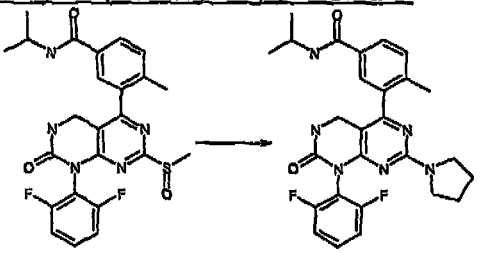


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (50 mg, 0.10 mmol) in DCM (5 mL) was added hexahydro-1*H*-azepine (0.034 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided

the title compound as a white solid (39 mg, 73%). LC-MS m/z 535 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.47 (m, 6 H), 1.70 (m, 2 H), 2.31 (s, 3H), 3.32 (m, 2 H), 3.68 (m, 2 H), 4.11 (m, 2 H), 4.23 (m, 1 H), 7.13 (t, 2 H), 7.44 (d, 1 H), 7.48 (m, 1 H), 7.69 (s, 1 H), 7.85 (d, 1 H).

Example 67

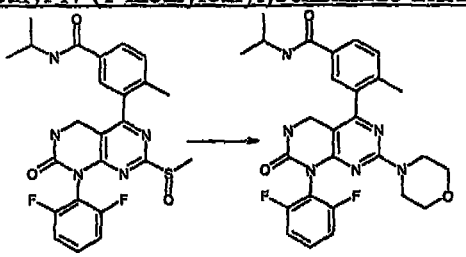
3-[8-(2,6-difluorophenyl)-7-oxo-2-(1-pyrrolidinyl)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (50 mg, 0.10 mmol) in DCM (5 mL) was added pyrrolidine (0.025 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (34 mg, 67%). LC-MS m/z 507 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.87 (m, 4 H), 2.31 (s, 3H), 3.33 (m, 4 H), 4.11 (m, 2 H), 4.23 (m, 1 H), 7.13 (t, 2 H), 7.44 (d, 1 H), 7.48 (m, 1 H), 7.70 (s, 1 H), 7.85 (d, 1 H).

Example 68

3-[8-(2,6-difluorophenyl)-2-(4-morpholinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

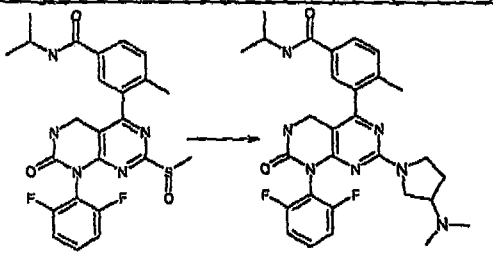


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (50 mg, 0.10 mmol) in DCM (5 mL) was added morpholine (0.026 mL, 0.30 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Gilson with TFA provided the title

compound as a white solid (40 mg, 76%). LC-MS m/z 523 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.30 (s, 3 H), 3.33 (m, 4H), 3.52 (m, 4 H), 4.18 (s, 2 H), 4.23 (m, 1 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.50 (m, 1 H), 7.71 (s, 1 H), 7.85 (d, 1 H).

Example 69

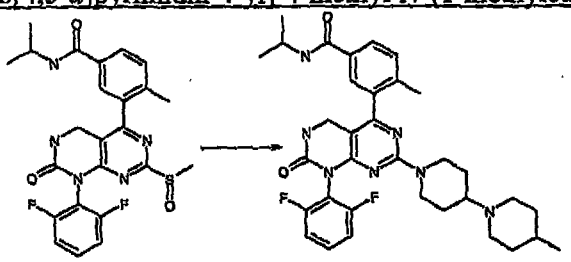
3-{8-(2,6-difluorophenyl)-2-[3-(dimethylamino)-1-pyrrolidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)-benzamide (30 mg, 0.06 mmol) in THF (1 mL)/$CHCl_3$ (1 mL) were added *N,N*-dimethyl-3-pyrrolidinamine (14 mg, 0.12 mmol) and *N,N*-diisopropylethylamine (0.6 mL, 3.0 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (25 mg, 76%). LC-MS m/z 550 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.75 (m, 1 H), 2.15 (m, 1H), 2.24 (s, 6 H), 2.30 (s, 3 H), 2.79 (m, 1 H), 3.15 (m, 2 H), 3.45 (m, 1H), 3.71 (m, 1 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.50 (m, 1 H), 7.70 (s, 1 H), 7.85 (d, 1 H).

Example 70

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1,4'-bipiperidin-1'-yl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide

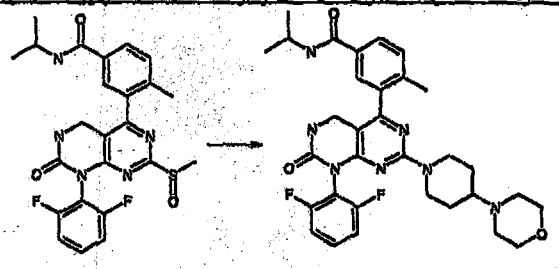


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added 4-methyl-1,4'-bipiperidine (40 mg, 0.22 mmol) and *N,N*-

diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (31 mg, 70%). LC-MS m/z 618 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (d, 3 H), 1.22 (m, 2 H), 1.27 (d, 6 H), 1.38 (m, 3 H), 1.68 (d, 2H), 1.81 (d, 2 H), 2.19 (t, 2 H), 2.30 (s, 3 H), 2.50 (t, 1 H), 2.71 (t, 2H), 2.93 (d, 2 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 4.45 (m, 2 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.50 (m, 1 H), 7.68 (s, 1 H), 7.85 (d, 1 H).

Example 71

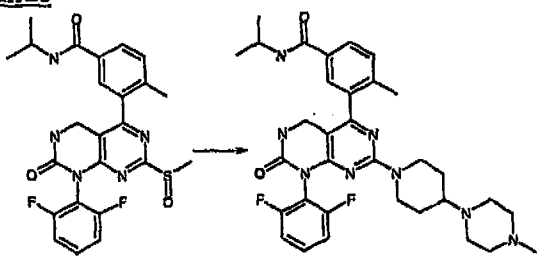
3-{8-(2,6-difluorophenyl)-2-[4-(4-morpholinyl)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added 4-(4-piperidinyl)morpholine (37 mg, 0.22 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (41 mg, 94%). LC-MS m/z 607 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.33 (m, 2 H), 1.83 (d, 2H), 2.30 (s, 3 H), 2.38 (m, 1 H), 2.55 (m, 4 H), 2.75 (t, 2 H), 3.33 (m, 1H), 3.68 (m, 3 H), 4.11 (s, 2 H), 4.23 (m, 1 H), 4.45 (m, 2 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.50 (m, 1 H), 7.68 (s, 1 H), 7.85 (d, 1 H).

Example 72

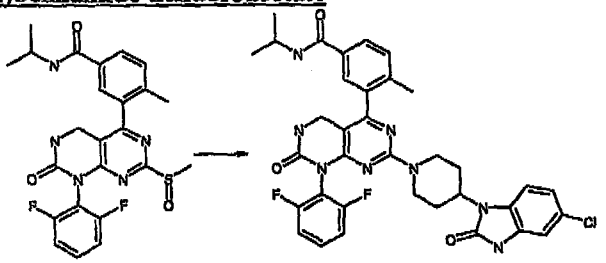
3-{8-(2,6-difluorophenyl)-2-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added 1-methyl-4-(4-piperidinyl)piperazine (40 mg, 0.22 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (38 mg, 85%). LC-MS m/z 619 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.33 (m, 2 H), 1.83 (d, 2H), 2.28 (s, 3 H), 2.30 (s, 3 H), 2.65 (m, 11 H), 4.11 (m, 2 H), 4.23 (m, 1 H), 4.45 (m, 2 H), 7.16 (t, 2 H), 7.46 (d, 1 H), 7.50 (m, 1 H), 7.68 (s, 1 H), 7.85 (d, 1 H).

Example 73

3-[2-[4-(5-chloro-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

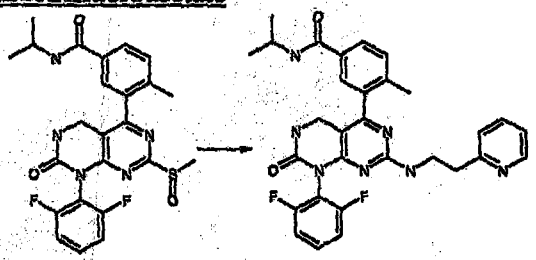


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added 5-chloro-1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one (51 mg, 0.22 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated.

HPLC with TFA separation provided the title compound as a white solid (44 mg, 89%). LC-MS m/z 688 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.75 (d, 2 H), 2.00 (m, 2H), 2.86 (m, 2 H), 2.36 (s, 3 H), 3.00 (d, 2 H), 4.18 (m, 2 H), 4.23 (m, 1 H), 4.46 (m, 1 H), 4.54 (m, 2 H), 7.06 (m, 2 H), 7.16 (m, 3 H), 7.50 (m, 2 H), 7.74 (s, 1 H), 7.88 (d, 1 H).

Example 74

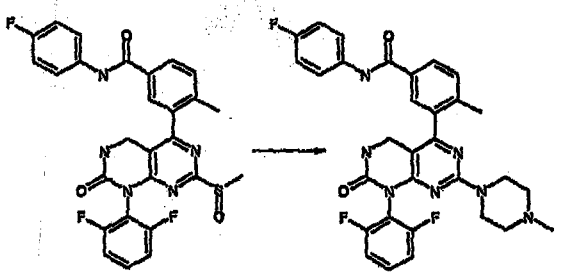
3-(8-(2,6-difluorophenyl)-7-oxo-2-{[2-(2-pyridinyl)ethyl]amino}-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamidetrifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added [2-(2-pyridinyl)ethyl]amine (0.026 mL, 0.22 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. HPLC with TFA, separation then provided the title compound as a white solid (40 mg, 98%). LC-MS m/z 568 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.30 (s, 3 H), 3.15 (m, 2 H), 3.65 (m, 2 H), 4.13 (m, 2 H), 4.23 (m, 1 H), 7.18 (m, 2 H), 7.51 (m, 2 H), 7.68 (m, 2 H), 7.90 (m, 2 H), 8.46 (m, 1 H), 8.67 (m, 1 H).

Example 75

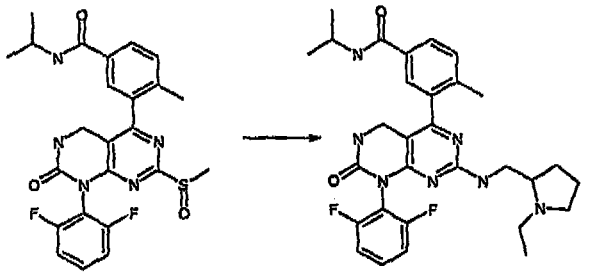
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide trifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide (26 mg, 0.047 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added 1-methylpiperazine (0.017 mL, 0.15 mmol) and *N,N*-diisopropylethylamine (0.03 mL, 0.015 mmol). The resultant solution was stirred at 50^0C over night. The result mixture was concentrated. Separation via a HPLC, with TFA then provided the title compound as a white solid (13 mg, 47 %). LC-MS m/z 588 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.34 (s, 3 H), 2.91 (s, 3 H), 3.11 (m, 2 H), 3.15 (m, 2 H), 3.45 (m, 2 H), 4.23 (m, 2 H), 4.54 (m, 2 H), 7.15 (m, 4 H), 7.55 (m, 2 H), 7.71 (m, 2 H), 7.82 (s, 1 H), 8.00 (d, 1 H).

Example 76

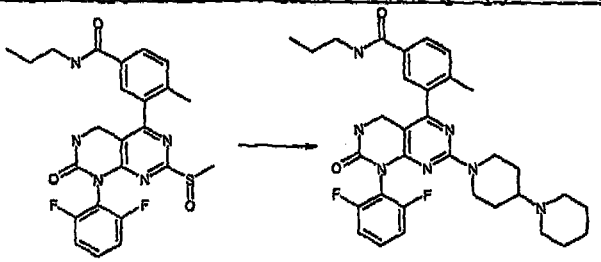
3-{8-(2,6-difluorophenyl)-2-{[(1-ethyl-2-pyrrolidinyl)methyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (36 mg, 0.072 mmol) in THF (2 mL)/ $CHCl_3$ (2mL) were added [(1-ethyl-2-pyrrolidinyl)methyl]amine (27.7 mg, 0.22 mmol) and *N,N*-diisopropylethylamine (0.1 mL, 0.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Purification via a HPLC with TFA then provided the title compound as a white solid (30 mg, 74%). LC-MS m/z 564 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 0.85 (m, 3 H), 1.27 (d, 6 H), 1.93 (m, 2 H), 2.06 (m, 2 H), 2.35 (s, 3 H), 2.88 (m, 1 H), 3.08 (m, 1 H), 3.28 (m, 1 H), 3.45 (m, 2 H), 3.51 (m, 2 H), 4.13 (m, 2 H), 4.23 (m, 1 H), 7.18 (m, 2 H), 7.51 (m, 2 H), 7.74 (s, 1 H), 7.90 (d, 1 H).

Example 77

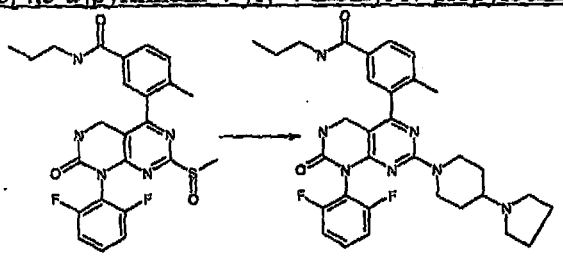
3-[2-(1,4'-bipiperidin-1'-yl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (17 mg, 0.034 mmol) in DCM (2 mL) was added 1,4'-bipiperidine (16 mg, 0.10 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (13 mg, 63%). LC-MS m/z 604 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3 H), 1.50 (m, 4 H), 1.68 (m, 6 H), 1.92 (m, 2 H), 2.31 (s, 3 H), 2.73 (m, 2 H), 2.90 (m, 5 H), 3.37 (m, 2 H), 4.16 (m, 2 H), 4.52 (m, 2 H), 7.16 (m, 2 H), 7.46 (m, 1 H), 7.51 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 78

3-{8-(2,6-difluorophenyl)-7-oxo-2-[4-(1-pyrrolidinyl)-1-piperidinyl]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-propylbenzamide

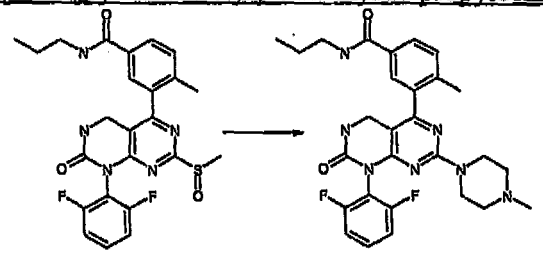


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (17 mg, 0.034 mmol) in DCM (2 mL) was added 4-(1-pyrrolidinyl)piperidine (15 mg, 0.10 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (11 mg, 55%). LC-MS m/z 592 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3 H), 1.34 (m, 2 H), 1.68 (m, 3 H), 1.90 (m, 5 H), 2.31 (s, 3 H), 2.36 (m, 1 H), 2.68 (m, 6

H), 3.37 (m, 2 H), 4.11 (m, 2 H), 4.42 (m, 2 H), 7.16 (m, 2 H), 7.46 (m, 1 H), 7.51 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 79

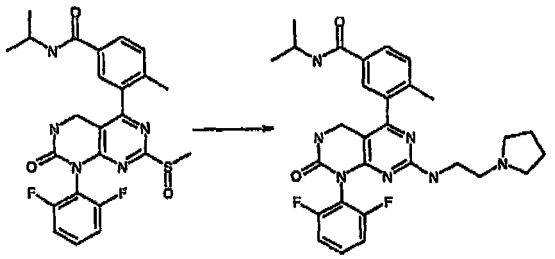
3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-propylbenzamide (17 mg, 0.034 mmol) in DCM (2 mL) was added 1-methylpiperazine (0.011 mL, 0.10 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (11 mg, 60%). LC-MS m/z 536 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3 H), 1.66 (m, 2 H), 2.28 (s, 3 H), 2.31 (s, 3 H), 2.42 (m, 4 H), 3.37 (m, 2 H), 3.57 (m, 4 H), 4.13 (m, 2 H), 7.16 (m, 2 H), 7.46 (m, 1 H), 7.51 (m, 1 H), 7.68 (s, 1 H), 7.86 (d, 1 H).

Example 80

3-(8-(2,6-difluorophenyl)-7-oxo-2-{[2-(1-pyrrolidinyl)ethyl]amino}-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

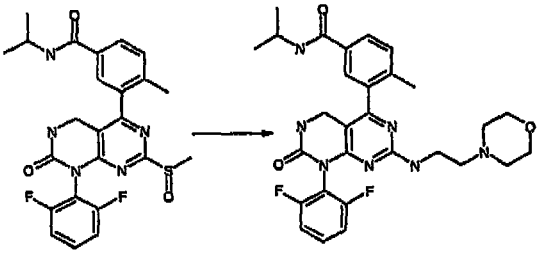


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added [2-(1-pyrrolidinyl)ethyl]amine (0.025 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA provided the title compound as a white solid (10 mg, 45%). LC-

MS m/z 550 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.70 (m, 2 H), 2.04 (m, 2 H), 2.31 (s, 3 H), 2.91 (m, 2 H), 3.26 (m, 2 H), 3.53 (m, 4 H), 4.16 (m, 2 H), 4.23 (m, 1 H),7.18 (m, 2 H), 7.48 (m, 1 H), 7.54 (m, 1 H), 7.71 (s, 1 H), 7.86 (d, 1 H).

Example 81

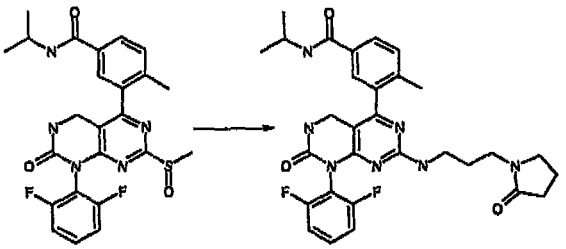
3-(8-(2,6-difluorophenyl)-2-{[2-(4-morpholinyl)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added [2-(4-morpholinyl)ethyl]amine (0.026 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (11 mg, 49%). LC-MS m/z 566 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.33 (s, 3 H), 3.14 (m, 2 H), 3.22 (m, 3 H), 3.58 (m, 5 H), 3.90 (m, 2 H), 4.16 (m, 2 H), 4.23 (m, 1 H),7.18 (m, 2 H), 7.50 (m, 1 H), 7.54 (m, 1 H), 7.74 (s, 1 H), 7.88 (d, 1 H).

Example 82

3-(8-(2,6-difluorophenyl)-7-oxo-2-{[3-(2-oxo-1-pyrrolidinyl)propyl]amino}-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

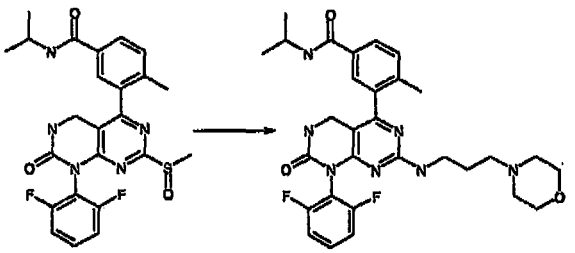


To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added 1-(3-aminopropyl)-2-pyrrolidinone (0.028 mL, 0.20 mmol). The resultant solution was

stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (10 mg, 43%). LC-MS m/z 578 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.66 (m, 2 H), 2.05 (m, 2 H), 2.35 (m, 2 H), 2.39 (s, 3 H), 3.16 (m, 4 H), 3.40 (m, 2 H), 4.16 (m, 2 H), 4.23 (m, 1 H),7.22 (m, 2 H), 7.55 (m, 1 H), 7.62 (m, 1 H), 7.83 (s, 1 H), 7.95 (d, 1 H).

Example 83

3-(8-(2,6-difluorophenyl)-2-{[3-(4-morpholinyl)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



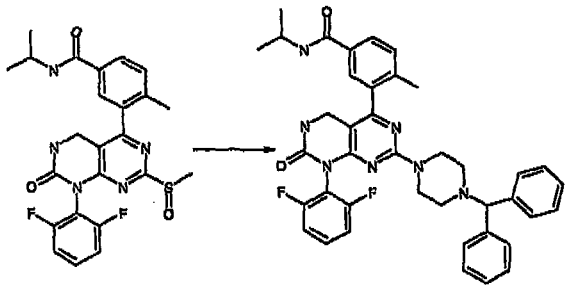
To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added [3-(4-morpholinyl)propyl]amine (0.029 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (10 mg, 43%). LC-MS m/z 580 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 1.87 (m, 2 H), 2.33 (s, 3 H), 3.14 (m, 4 H), 3.30 (m, 2 H), 3.39 (m, 2 H), 3.68 (m, 2 H), 4.01 (m, 2 H), 4.16 (m, 2 H), 4.23 (m, 1 H),7.18 (m, 2 H), 7.48 (m, 1 H), 7.55 (m, 1 H), 7.72 (s, 1 H), 7.89 (d, 1 H).

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Example 84

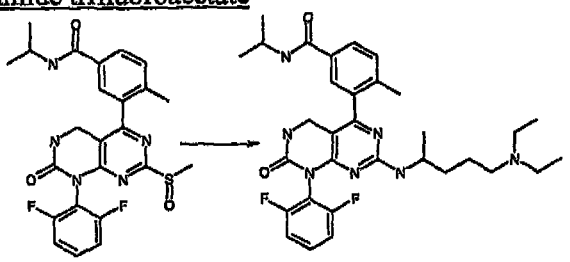
3-{8-(2,6-difluorophenyl)-2-[4-(diphenylmethyl)-1-piperazinyl]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added 1-(diphenylmethyl)piperazine (50 mg, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (13 mg, 47%). LC-MS m/z 688 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.28 (s, 3 H), 3.17 (m, 5 H), 3.70 (m, 3 H), 4.18 (m, 2 H), 4.23 (m, 1 H), 5.39 (m, 1 H),7.13 (m, 2 H), 7.45 (m, 8 H), 7.59 (m, 4 H), 7.66 (s, 1 H), 7.85 (d, 1 H).

Example 85

3-[2-{[4-(diethylamino)-1-methylbutyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



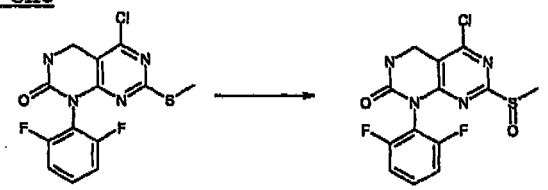
To a solution of compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in DCM (2 mL) was added N^1,N^1-diethyl-1,4-pentanediamine (0.039 mL, 0.20 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (7 mg, 29%). LC-MS m/z 594 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.10 (d, 3 H), 1.27 (m,

12 H), 1.51 (m, 2 H), 1.65 (m, 2 H), 2.34 (s, 3 H), 3.02 (m, 2 H), 3.17 (m, 4 H), 3.38 (m, 1 H), 4.16 (m, 2 H), 4.23 (m, 1 H),7.18 (m, 2 H), 7.48 (m, 1 H), 7.54 (m, 1 H), 7.72 (s, 1 H), 7.89 (d, 1 H).

Example 86

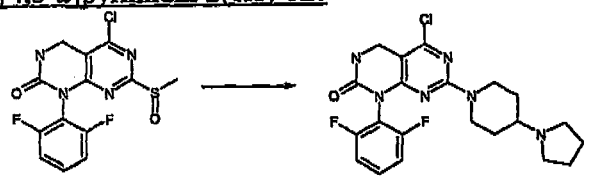
3-{8-(2,6-difluorophenyl)-7-oxo-2-[4-(1-pyrrolidinyl)-1-piperidinyl]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

86a) 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (1.71 g, 5 mmol) in CH_2Cl_2 (60 mL) was added m-CPBA (1.17 g, 5.2 mmol). The mixture was stirred at room temperature for 10 minutes, then directly loaded onto a column. Flash chromatography (mobile phase EtOAc/Hexane) afforded the title compound as a white solid 1.58 g (88 %). LC-MS m/z 358 $(M + H)^+$.

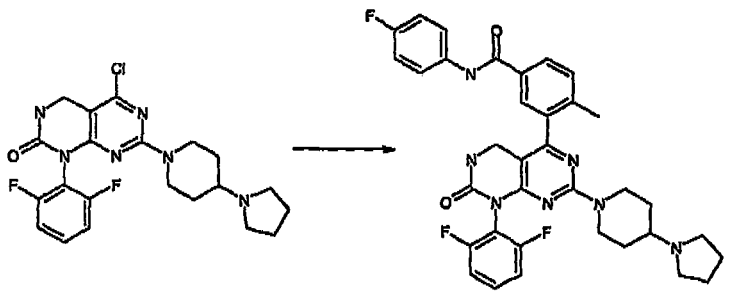
86b) 5-chloro-1-(2,6-difluorophenyl)-7-[4-(1-pyrrolidinyl)-1-piperidinyl]-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To a solution of the title compound from Example 86a (250 mg, 0.70 mmol) in DCM (10 mL) were added 4-(1-pyrrolidinyl)piperidine (323 mg, 2.1 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 1.7 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (253 mg, 81 %). LC-MS m/z 449 $(M + H)^+$.

86c) 3-{8-(2,6-difluorophenyl)-7-oxo-2-[4-(1-pyrrolidinyl)-1-piperidinyl]-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-*N*-(4-fluorophenyl)-4-methylbenzamide

201

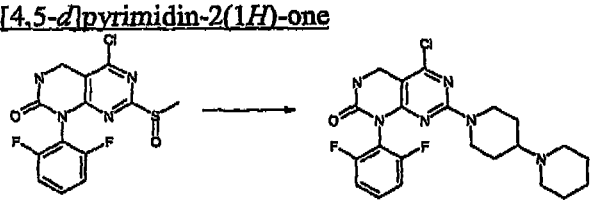


To a solution of the title compound from Example 86b (18 mg, 0.04 mmol) in dioxane (1.5 mL)/water (0.5 mL) were added potassium carbonate (34 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (2.3 mg, 0.002 mmol) and *N*-(4-fluorophenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (22 mg, 0.062 mmol). The reaction mixture was bubbled with N_2 for 5 mins, then microwaved at 150°C for 30 mins. The reaction mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+ NH_4OH[3]) provided the title compound as a white solid (14 mg, 54%). LC-MS m/z 642 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.32 (m, 2 H), 1.80 (m, 4 H), 1.88 (m, 2 H), 2.24 (m, 1 H), 2.33 (s, 3 H), 2.62 (m, 4 H), 2.74 (t, 2 H), 4.17 (m, 2 H), 4.40 (m, 2 H),7.12 (m, 4 H), 7.52 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 87

3-[2-(1,4'-bipiperidin-1'-yl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

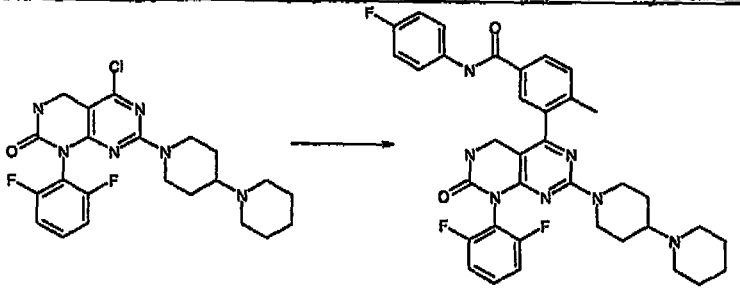
87a) 7-(1,4'-bipiperidin-1'-yl)-5-chloro-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.56 mmol) in DCM (10 mL) were added 1,4'-bipiperidine (270 mg, 1.61 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 1.7 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (298 mg, 83 %). LC-MS m/z 463 $(M + H)^+$.

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87b) 3-[2-(1,4'-bipiperidin-1'-yl)-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*-(4-fluorophenyl)-4-methylbenzamide

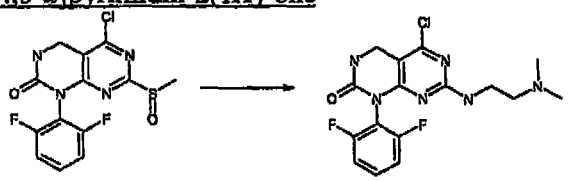


To a solution of compound 7-(1,4'-bipiperidin-1'-yl)-5-chloro-1-(2,6-difluorophenyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (18 mg, 0.04 mmol) in dioxane (1.5 mL)/water (0.5 mL) were added potassium carbonate (34 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (2.3 mg, 0.002 mmol) and *N*-(4-fluorophenyl)-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (22 mg, 0.062 mmol).The reaction mixture was bubbled with N_2 for 5 mins, then microwaved at 150^{0}C for 30 mins. The reaction mixture was concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH [7]+NH_4OH[3]) provided the title compound as a white solid (13 mg, 51%). LC-MS m/z 656 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.37 (m, 2 H), 1.48 (m, 2 H), 1.60 (m, 4 H), 1.80 (m, 2 H), 2.33 (s, 3 H), 2.56 (m, 5 H), 2.72 (t, 2 H), 4.17 (m, 2 H), 4.46 (m, 2 H),7.12 (m, 4 H), 7.52 (m, 2 H), 7.72 (m, 2 H), 7.82 (s, 1 H), 7.98 (d, 1 H).

Example 88

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(1-methylethyl)benzamide

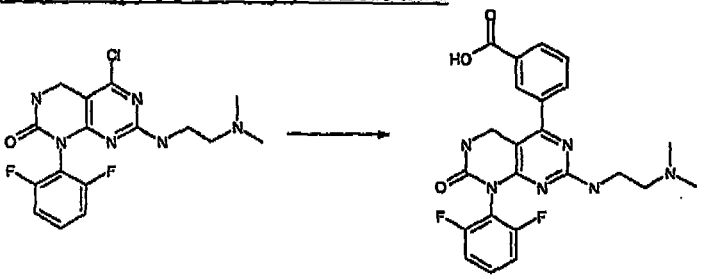
88a) 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one



To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-(methylsulfinyl)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (800 mg, 2.23 mmol) in DCM (45 mL) were added *N,N*-dimethylethylenediamine (0.36 mL, 3.23mmol) and triethylamine (0.63 mL, 4.5 mmol). The resultant solution was stirred at room temperature over night. The result mixture was concentrated. CombiFlash chromatography (mobile

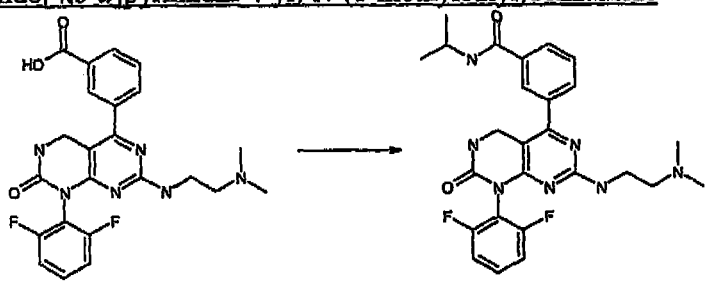
phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) provided the title compound as a white solid (730 mg, 85 %). LC-MS m/z 383 $(M + H)^+$.

88b) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid



To a solution of the title compound from Example 88a (100 mg, 0.26 mmol) in dioxane (9 mL)/water (3 mL) were added potassium carbonate (217 mg, 1.57 mmol), tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.013 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (65 mg, 0.39 mmol). The reaction mixture was bubbled with N_2 for 5 mins, then microwaved at 150^{0}C for 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H_2O (0.5 mL) and AcOH (0.05 mL). Separation via a HPLC then provided the title compound as a white solid (120 mg, 98%). LC-MS m/z 469 $(M + H)^+$.

88c) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(1-methylethyl)benzamide

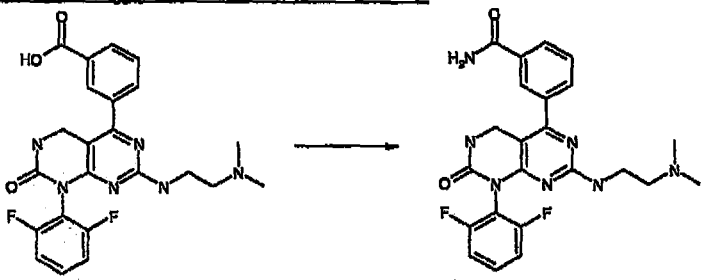


To the solution of the title compound from Example 88b (23 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) were added isopropylamine (0.005 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+ NH_4OH[3]) then provided the title compound as a white solid (20 mg, 80 %). LC-

MS m/z 510 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.16 (s, 6 H), 2.36 (m, 2 H), 3.28 (m, 2 H), 4.23 (m, 1 H), 4.46 (m, 2 H), 7.14 (m, 2 H), 7.49 (m, 1 H), 7.61 (m, 1 H), 7.72 (m, 1 H), 7.96 (d, 1 H), 8.00 (s, 1 H).

Example 89

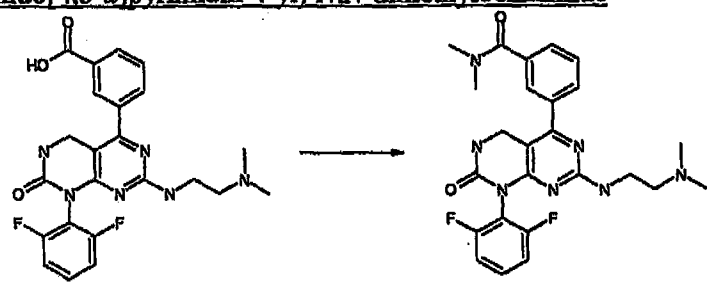
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (23 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) were added ammonia (2.0 M soln. in isopropanol, 0.0275 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (6 mg, 26 %). LC-MS m/z 468 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.16 (s, 6 H), 2.36 (m, 2 H), 3.20 (m, 2 H), 4.46 (s, 2 H), 7.14 (m, 2 H), 7.49 (m, 1 H), 7.61 (m, 1 H), 7.75 (m, 1 H), 8.00 (d, 1 H), 8.07 (s, 1 H).

Example 90

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*-dimethylbenzamide

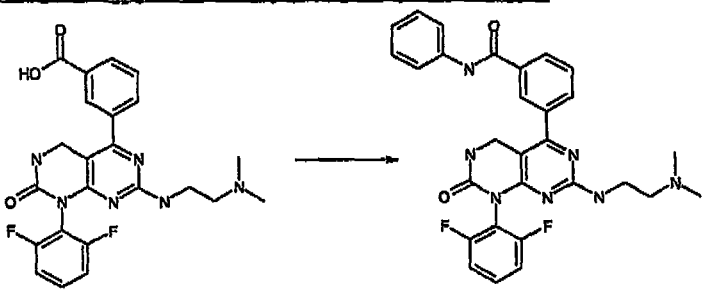


To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-

yl)benzoic acid (23 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) were added dimethylamine (2.0 M soln. in THF, 0.0275 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (10 mg, 41 %). LC-MS m/z 496 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.15 (s, 6 H), 2.36 (m, 2 H), 3.15 (s, 3 H), 3.06 (s, 3 H), 3.23 (m, 2 H), 4.46 (s, 2 H), 7.14 (m, 2 H), 7.12 (m, 1 H), 7.56 (m, 4 H).

Example 91

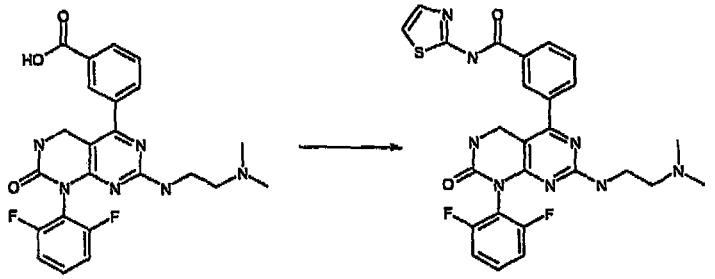
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-phenylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (23 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) were added aniline (0.005 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (15 mg, 56 %). LC-MS m/z 544 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.43 (s, 6 H), 2.70 (m, 2H), 3.48 (m, 2 H), 4.52 (s, 2 H), 7.17 (m, 3 H), 7.39 (m, 2 H), 7.52 (m, 1 H), 7.69 (m, 3 H), 7.79 (d, 1 H), 8.08 (d, 1 H), 8.15 (s, 1 H).

Example 92

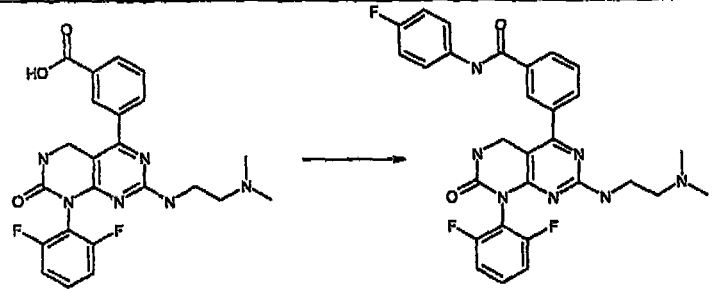
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl)-N-1,3-thiazol-2-ylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added 1,3-thiazol-2-amine (3.5 mg, 0.035 mmol), HATU (13 mg, 0.034 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+ MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (7 mg, 40 %). LC-MS m/z 551 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.22 (s, 6 H), 2.46 (m, 2H), 3.16 (m, 2 H), 4.51 (s, 2 H), 7.17 (m, 3 H), 7.51 (m, 2 H), 7.69 (m, 1 H), 7.83 (d, 1 H), 8.16 (d, 1 H), 8.23 (s, 1 H).

Example 93

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)benzamide

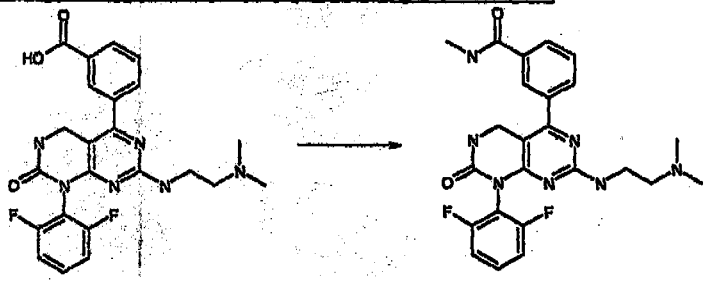


To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added 4-flouroaniline (0.003 mL, 0.035 mmol), HATU (13 mg, 0.034 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with

CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+ MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (13 mg, 72 %). LC-MS m/z 562 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.81 (s, 6 H), 3.21 (m, 2H), 3.59 (m, 2 H), 4.53 (s, 2 H), 7.17 (m, 4 H), 7.53 (m, 1 H), 7.72 (m, 3 H), 7.80 (d, 1 H), 8.10 (d, 1 H), 8.16 (s, 1 H).

Example 94

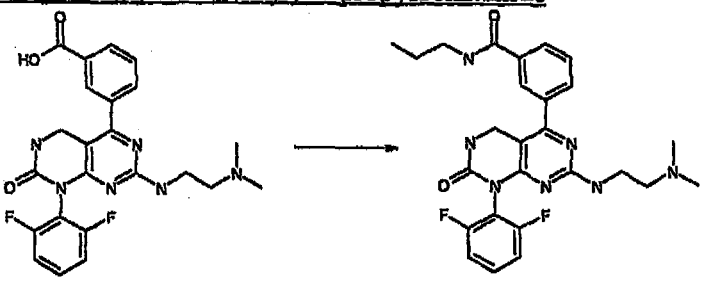
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-methylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added methylamine (2.0 M soln. in THF, 0.018 mL, 0.036 mmol), HATU (13 mg, 0.034 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (10 mg, 65 %). LC-MS m/z 482 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.16 (s, 6 H), 2.38 (m, 2H), 2.96 (s, 3 H), 3.22 (m, 2 H), 4.45 (s, 2 H), 7.16 (m, 2 H), 7.50 (m, 1 H), 7.64 (m, 1 H), 7.74 (d, 1 H), 7.95 (d, 1 H), 8.00 (s, 1 H).

Example 95

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-propylbenzamide

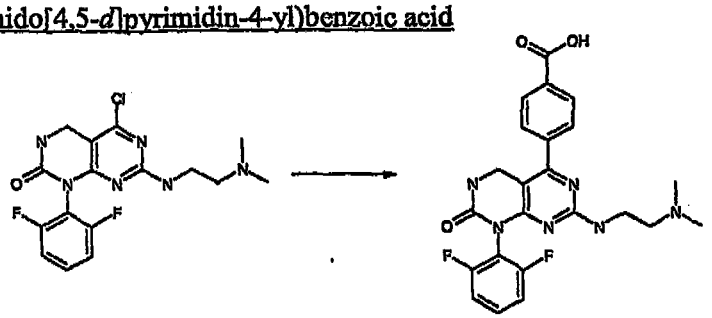


To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added propylamine (0.003 mL, 0.035 mmol), HATU (13 mg, 0.034 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7]+NH_4OH[3]) then provided the title compound as a white solid (5 mg, 31 %). LC-MS m/z 510 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.00 (t, 3 H), 1.67 (m, 2H), 2.80 (s, 6 H), 3.25 (m, 2 H), 3.40 (m, 2 H), 3.62 (m, 2 H), 4.52 (s, 2 H), 7.19 (m, 1 H), 7.53 (m, 1 H), 7.65 (m, 1 H), 7.76 (d, 1 H), 7.98 (d, 1 H), 8.05 (s, 1 H).

Example 96

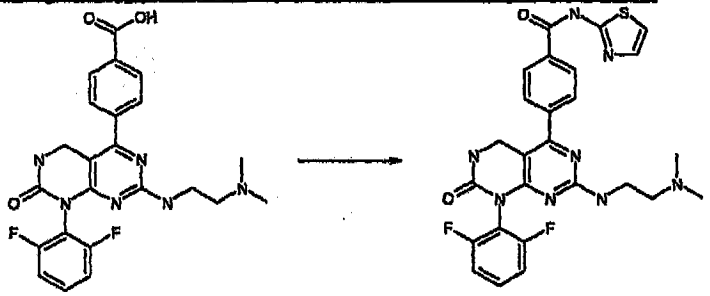
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-1,3-thiazol-2-ylbenzamide

96a) 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid



To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]-amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (150 mg, 0.39 mmol) in dioxane (12 mL)/water (4 mL) were added potassium carbonate (325 mg, 2.36 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.019 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (146 mg, 0.59 mmol). The reaction mixture was bubbled with N_2 for 5 mins, then microwaved at 150^{0}C for 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H_2O (0.5 mL) and AcOH (0.05 mL). Separation via a HPLC then provided the title compound as a white solid (142 mg, 77%). LC-MS m/z 469 $(M + H)^+$.

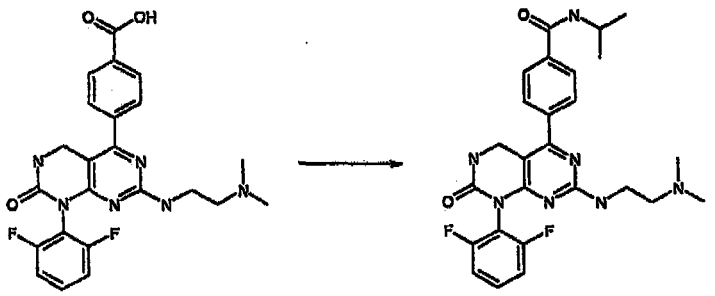
96b) 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-1,3-thiazol-2-ylbenzamide



To the solution of the title compound from Example 96a (15 mg, 0.03 mmol) in DMF (3 mL) were added 1,3-thiazol-2-amine (3.5 mg, 0.035 mmol), HATU (13 mg, 0.035 mmol) and diisopropyl ethyl amine (0.05 mL, 0.3 mmol). The reaction mixture was stirred over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL) and shaked. The layers were separated and the organic layer was washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated. CombiFlash chromatography (mobile phase DCM/DCM[90]+MeOH[7] +NH_4OH[3]) then provided the title compound as a white solid (7 mg, 40 %). LC-MS m/z 551 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.83 (s, 6 H), 3.15 (m, 2 H), 3.51 (m, 2 H), 4.52 (s, 2 H), 7.17 (m, 3 H), 7.53 (m, 2 H), 7.77 (m, 2 H), 8.19 (m, 2 H).

Example 97

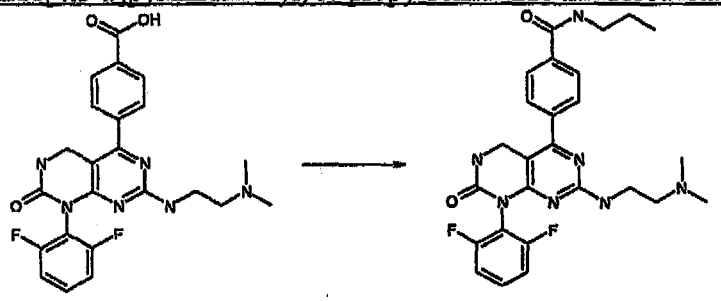
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(1-methylethyl)benzamide trifluoroacetate



To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added isopropylamine (0.0085 mL, 0.1 mmol) and HATU (13 mg, 0.035 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (5 mg, 31 %). LC-MS m/z 510 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.29 (d, 6 H), 2.79 (s, 6 H), 3.22 (m, 2 H), 3.59 (m, 2 H), 4.26 (m, 1 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.54 (m, 1 H), 7.67 (m, 2 H), 7.99 (m, 2 H).

Example 98

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-propylbenzamide trifluoroacetate

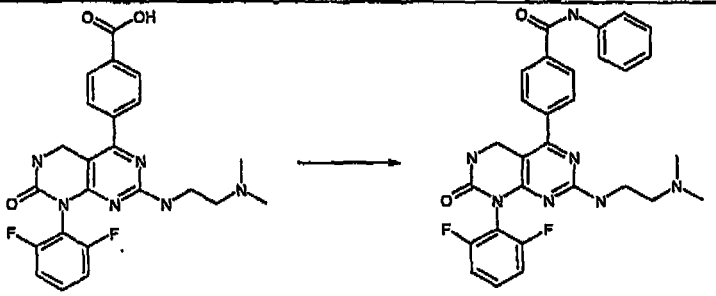


To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added propylamine (0.0082 mL, 0.1 mmol) and HATU (13 mg, 0.035 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (5 mg, 31 %). LC-MS m/z 510 $(M + H)^+$; ^{1}H-

NMR (MeOD) δ 1.02 (t, 3 H), 1.68 (m, 2 H), 2.79 (s, 6 H), 3.22 (m, 2 H), 3.59 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.54 (m, 1 H), 7.68 (m, 2 H), 7.99 (m, 2 H).

Example 99

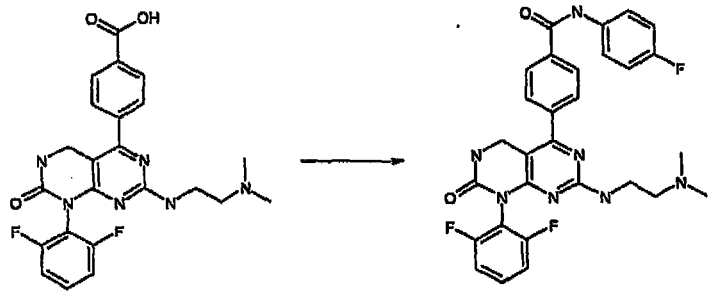
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-phenylbenzamide trifluoroacetate



To the solution of -(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added aniline (0.0091 mL, 0.1 mmol) and HATU (13 mg, 0.035 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (7 mg, 40 %). LC-MS m/z 544 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.80 (s, 6 H), 3.21 (m, 2 H), 3.59 (m, 2 H), 4.53 (s, 2 H), 7.18 (m, 3 H), 7.40 (m, 2 H), 7.52 (m, 1 H), 7.72 (m, 4 H), 8.12 (m, 2 H).

Example 100

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)benzamide trifluoroacetate

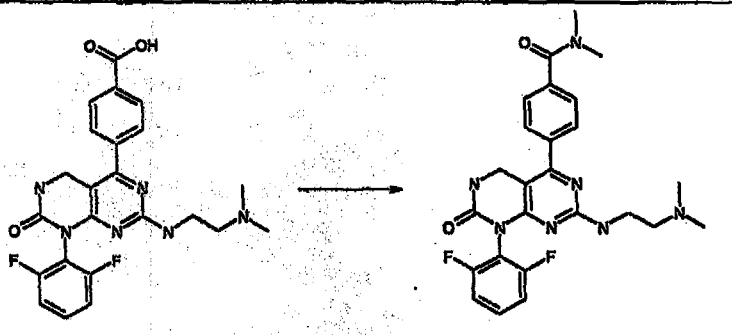


To the solution of -(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (15 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) were added 4-flouroaniline (0.0096 mL, 0. 1 mmol) and HATU (13 mg, 0.035 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA

then provided the title compound as a white solid (7 mg, 39 %). LC-MS m/z 562 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.80 (s, 6 H), 3.19 (m, 2 H), 3.59 (m, 2 H), 4.53 (s, 2 H), 7.17 (m, 4 H), 7.52 (m, 1 H), 7.72 (m, 4 H), 8.12 (m, 2 H).

Example 101

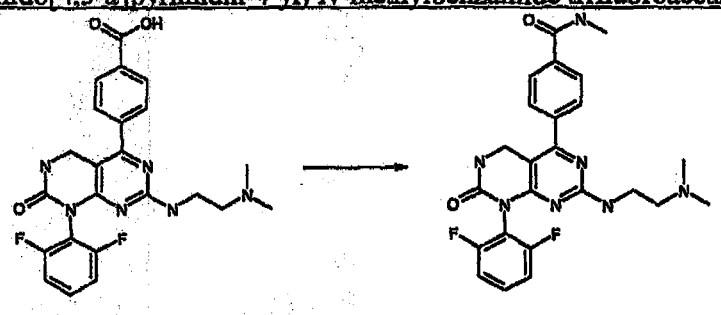
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*-dimethylbenzamide trifluoroacetate



To the solution of -(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (20 mg, 0.043 mmol) in CH_2Cl_2 (2 mL) were added dimethylamine (2.0 M soln. in THF, 0.064 mL, 0.13 mmol) and HATU (17.2 mg, 0.045 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (18 mg, 85 %). LC-MS m/z 496 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.79 (s, 6 H), 3.06 (s, 3 H), 3.16 (s, 3 H), 3.22 (m, 2 H), 3.58 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.54 (m, 1 H), 7.61 (m, 2 H), 7.71 (m, 2 H).

Example 102

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-methylbenzamide trifluoroacetate

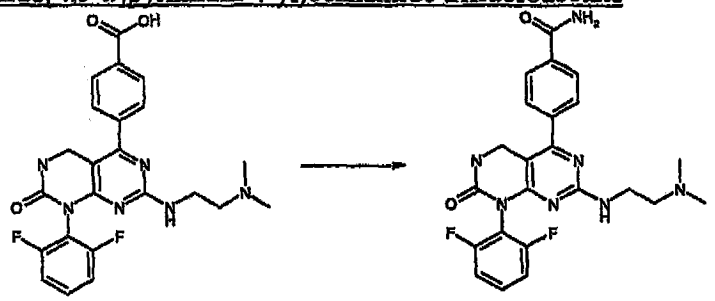


To the solution of -(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (20 mg, 0.043 mmol) in CH_2Cl_2 (2 mL) were added methylamine (2.0 M soln. in THF,

0.064 mL, 0.13 mmol) and HATU (17.2 mg, 0.045 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (3 mg, 15 %). LC-MS m/z 482 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.79 (s, 6 H), 2.98 (s, 3 H), 3.26 (m, 2 H), 3.59 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.53 (m, 1 H), 7.68 (m, 2 H), 7.99 (m, 2 H).

Example 103

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzamide trifluoroacetate

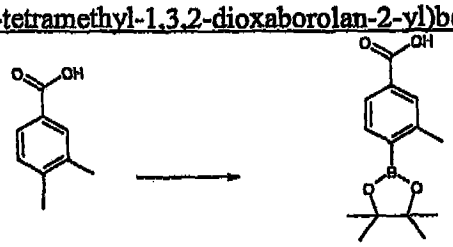


To the solution of -(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)benzoic acid (20 mg, 0.043 mmol) in CH_2Cl_2 (2 mL) were added ammonia (2.0 M soln. in propanol, 0.064 mL, 0.13 mmol) and HATU (17.2 mg, 0.045 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (18 mg, 90 %). LC-MS m/z 468 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.79 (s, 6 H), 3.18 (m, 2 H), 3.58 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.53 (m, 1 H), 7.71 (m, 2 H), 8.05 (m, 2 H).

Example 104

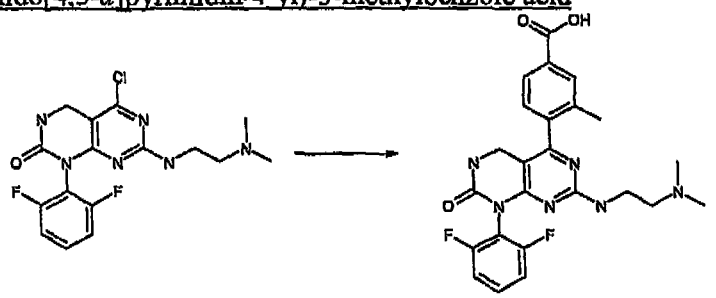
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate

104a) 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid



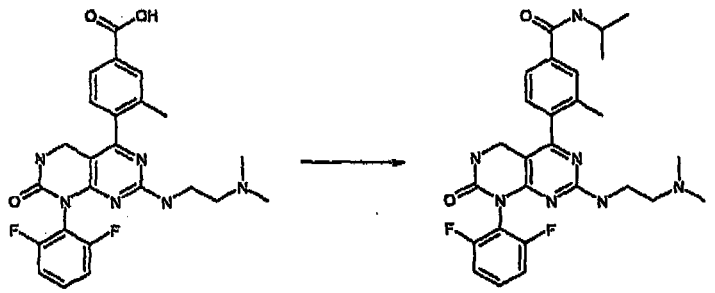
To a solution of 4-iodo-3-methylbenzoic acid (520 mg, 2.0 mmol) in DMF (8 mL) were added palladium acetate (23 mg, 0.10 mmol), potassium acetate (590 mg, 6.0 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (560 mg, 2.2 mmol). The reaction mixture was microwaved at 150°C for 30 mins. The reaction mixture was poured into water (25 mL), extracted with ethylacetate (100 mL) while acetic acid (1 mL) was added. The organic layer was washed with water (50 mL), brine (50 mL), dried with sodium sulfate, filtered and concentrated. The residue was separated by combiflash which provided the title compound as a white solid (460 mg, 88%). LC-MS m/z 263 $(M + H)^+$.

104b) 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid



To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]-amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.52 mmol) in dioxane (15 mL)/water (5 mL) were added potassium carbonate (433 mg, 3.14 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.027 mmol) and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (205 mg, 0.78 mmol). The reaction mixture was bubbled with N_2 for 10 mins, then microwaved at 150°C for 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H_2O (0.5 mL) and AcOH (0.05 mL). Gilson with TFA provided the title compound as a white solid (310 mg, 99%). LC-MS m/z 483 $(M + H)^+$.

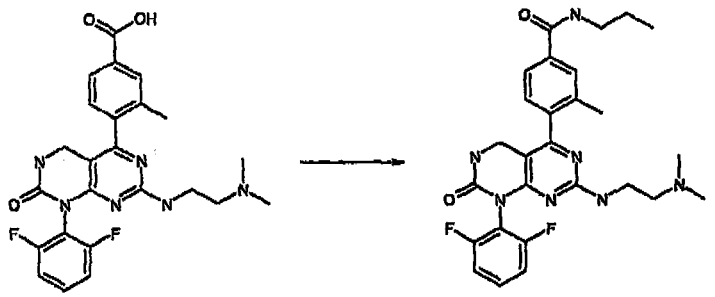
104c) 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-(1-methylethyl)benzamide trifluoroacetate



To the solution of the title compound from Example 104b (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added isopropylamine (0.022 mL, 0.25 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFAthen provided the title compound as a white solid (17 mg, 63 %). LC-MS m/z 524 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.29 (d, 6 H), 2.34 (s, 3 H), 2.76 (s, 6 H), 3.16 (m, 2 H), 3.55 (m, 2 H), 4.15 (s, 2 H), 4.25 (m, 1 H), 7.21 (m, 2 H), 7.36 (m, 1 H), 7.55 (m, 1 H), 7.78 (d, 1 H), 7.84 (s, 1 H).

Example 105

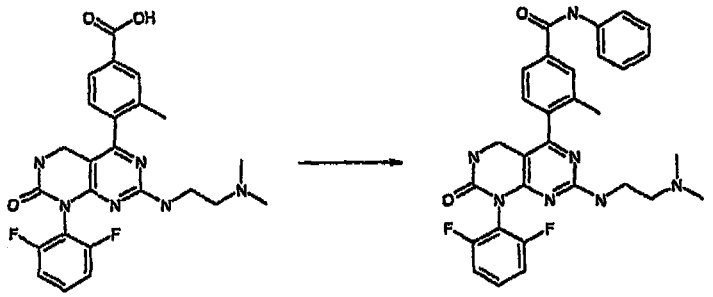
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-propylbenzamide trifluoroacetate



To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added propylamine (0.021 mL, 0.25 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (7 mg, 26 %). LC-MS m/z 524 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.01 (t, 3 H), 1.67 (m, 2 H), 2.33 (s, 3 H), 2.76 (s, 6 H), 3.16 (m, 2 H), 3.55 (m, 2 H), 4.15 (s, 2 H), 7.18 (m, 2 H), 7.36 (m, 1 H), 7.55 (m, 1 H), 7.78 (d, 1 H), 7.84 (s, 1 H).

Example 106

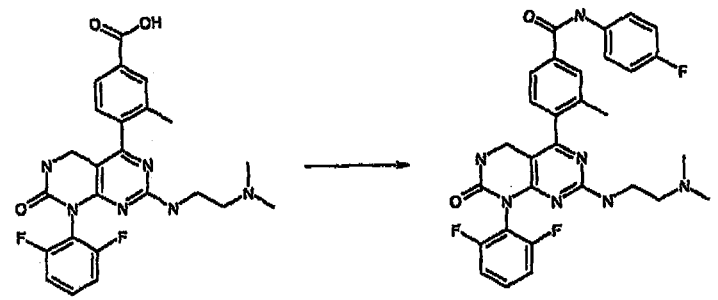
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methyl-*N*-phenylbenzamide trifluoroacetate



To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added aniline (0.024 mL, 0.25 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (23 mg, 79 %). LC-MS m/z 558 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.38 (s, 3 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.55 (m, 2 H), 4.17 (s, 2 H), 7.21 (m, 3 H), 7.42 (m, 3 H), 7.55 (m, 1 H), 7.72 (m, 2 H), 7.89 (m, 1 H), 7.97 (s, 1 H).

Example 107

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(4-fluorophenyl)-3-methylbenzamide trifluoroacetate



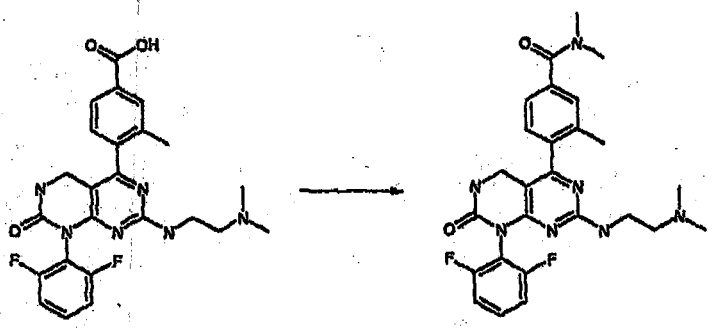
To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added 4-flouroaniline (0.025 mL, 0.25 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (22 mg, 74 %). LC-MS m/z 576

217

$(M+H)^+$; ^{1}H-NMR (MeOD) δ 2.37 (s, 3 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.55 (m, 2 H), 4.17 (s, 2 H), 7.16 (m, 4 H), 7.42 (m, 1 H), 7.55 (m, 1 H), 7.72 (m, 2 H), 7.89 (m, 1 H), 7.97 (s, 1 H).

Example 108

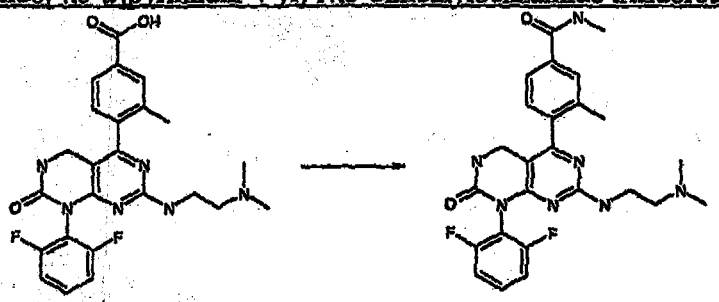
4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*,3-trimethylbenzamide trifluoroacetate



To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added dimethylamine (2.0 M soln. in THF, 0.13 mL, 0.26 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (19 mg, 72 %). LC-MS m/z 510 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 2.32 (s, 3 H), 2.77 (s, 6 H), 3.06 (s, 3 H), 3.15 (m, 5 H), 3.55 (m, 2 H), 4.17 (s, 2 H), 7.19 (m, 2 H), 7.37 (m, 2 H), 7.46 (s, 1 H), 7.55 (m, 1 H).

Example 109

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,3-dimethylbenzamide trifluoroacetate

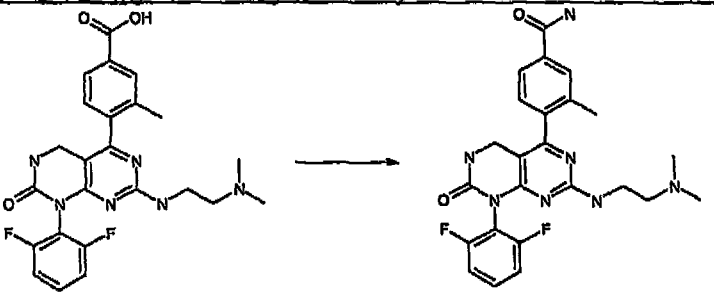


To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic

acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added methylamine (2.0 M soln. in THF, 0.13 mL, 0.26 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (3 mg, 12 %). LC-MS m/z 496 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.33 (s, 3 H), 2.76 (s, 6 H), 2.96 (s, 3 H), 3.15 (m, 2 H), 3.55 (m, 2 H), 4.15 (s, 2 H), 7.18 (m, 2 H), 7.36 (m, 1 H), 7.55 (m, 1 H), 7.76 (m, 1 H), 7.83 (s, 1 H).

Example 110

4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzamide trifluoroacetate

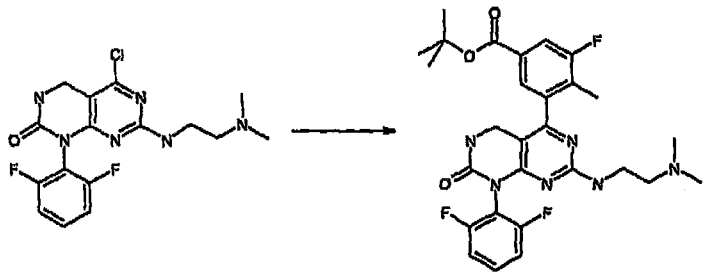


To the solution of 4-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-3-methylbenzoic acid (25 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) were added ammonia (2.0 M soln. in propanol, 0.13 mL, 0.26 mmol) and HBTU (21 mg, 0.055 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA then provided the title compound as a white solid (15 mg, 60 %). LC-MS m/z 482 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.33 (s, 3 H), 2.76 (s, 6 H), 3.15 (m, 2 H), 3.55 (m, 2 H), 4.15 (s, 2 H), 7.19 (m, 2 H), 7.36 (m, 1 H), 7.55 (m, 1 H), 7.84 (m, 1 H), 7.91 (s, 1 H).

Example 111

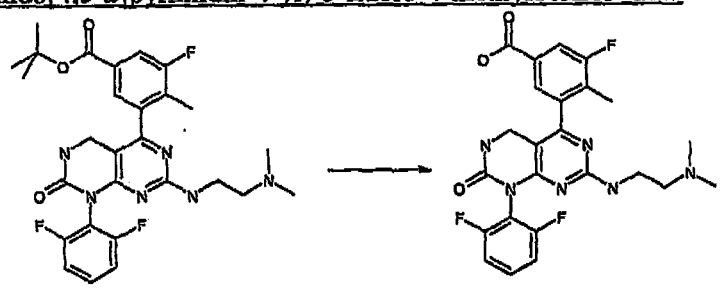
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide

111a) 1,1-dimethylethyl 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoate



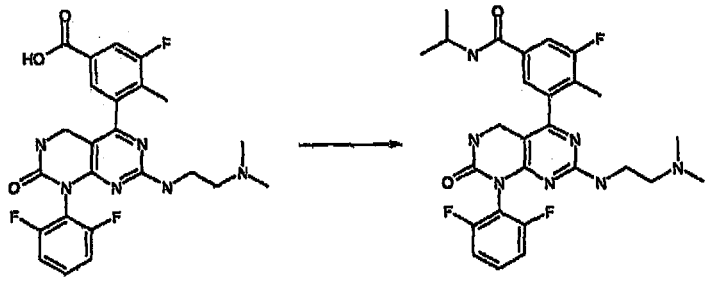
To a solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (200 mg, 0.52 mmol) in dioxane (15 mL)/water (5 mL) were added potassium carbonate (433 mg, 3.14 mmol), tetrakis(triphenylphosphine)palladium(0) (31 mg, 0.027 mmol) and (5-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-2-methylphenyl)boronic acid (159 mg, 0.63 mmol). The reaction mixture was bubbled with N_2 for 10 mins, then microwaved at 150°C for 30 mins. The reaction mixture was concentrated. To the concentrated mixture were added DMSO (2 mL), H_2O (0.5 mL) and AcOH (0.05 mL). Separation via a HPLC then provided the title compound as a white solid (270 mg, 88%). LC-MS m/z 587 $(M + H)^+$.

111b) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoic acid



To a solution of the title compound from Example 111a (260 mg, 0.45 mmol) in CH_2Cl_2 (1 mL) were added TFA (0.45 mL, 5.84 mmol) and triethylsilane (0.18 mL, 1.12 mmol). The reaction mixture was stirred overnight. The reaction mixture was concentrated. Separation via a HPLC then provided the title compound as a white solid (260 mg, 96%). LC-MS m/z 501 $(M + H)^+$.

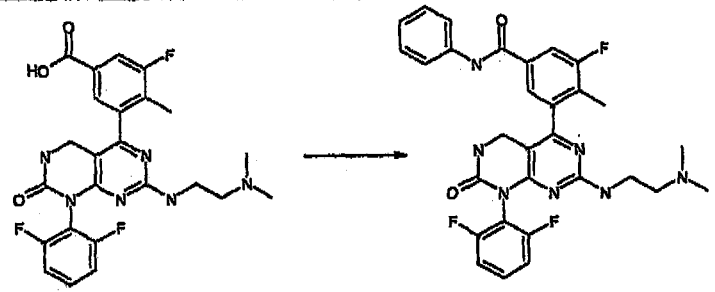
111c) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methyl-*N*-(1-methylethyl)benzamide



To the solution of the title compound from Example 111b (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were added isopropylamine (0.021 mL, 0.25 mmol) and HBTU (20 mg, 0.053 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (9 mg, 33 %). LC-MS m/z 542 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 1.27 (d, 6 H), 2.40 (s, 3 H), 2.78 (s, 6 H), 3.15 (m, 2 H), 3.55 (m, 2 H), 4.22 (m, 3 H), 7.18 (m, 2 H), 7.57 (m, 2 H), 7.71 (m, 1 H).

Example 112

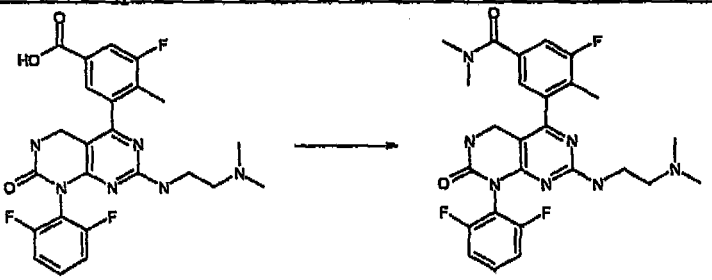
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methyl-*N*-phenylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoic acid (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were added aniline (0.025 mL, 0.25 mmol) and HBTU (20 mg, 0.053 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (10 mg, 35 %). LC-MS m/z 576 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 2.27 (s, 3 H), 2.79 (s, 6 H), 3.15 (m, 2 H), 3.55 (m, 2 H), 4.21 (s, 2 H), 7.19 (m, 3 H), 7.39 (m, 2 H), 7.54 (m, 1 H), 7.71 (m, 3 H), 7.86 (m, 1 H).

Example 113

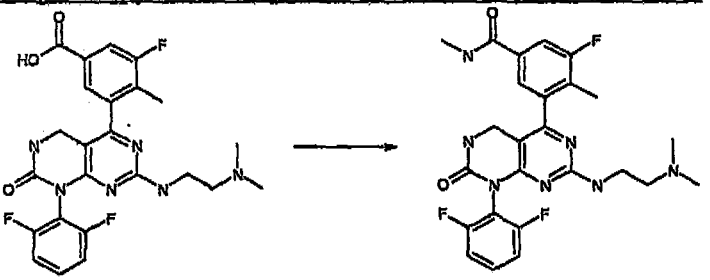
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-*N*,*N*,4-trimethylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoic acid (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were added dimethylamine (2.0 M soln. in THF, 0.13 mL, 0.26 mmol), triethylamine (0.05 mL, 0.36 mmol) and HBTU (20 mg, 0.053 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (15 mg, 57 %). LC-MS m/z 528 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.23 (s, 3 H), 2.78 (s, 6 H), 3.06 (s, 3 H), 3.15 (m, 5 H), 3.55 (m, 2 H), 4.22 (s, 2 H), 7.19 (m, 3 H), 7.34 (m, 1 H), 7.56 (m, 1 H).

Example 114

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-*N*,4-dimethylbenzamide

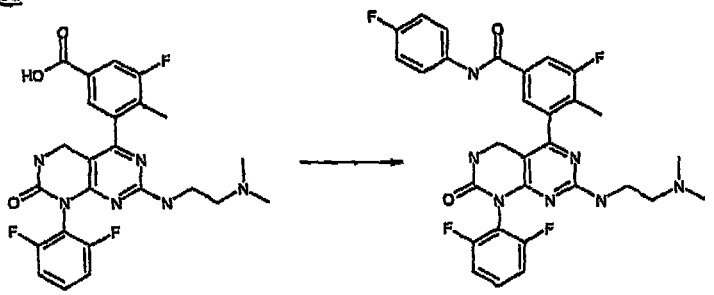


To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoic acid (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were added methylamine (2.0 M soln. in THF, 0.13 mL, 0.26 mmol), triethylamine (0.05 mL, 0.36 mmol) and HBTU (20 mg, 0.053 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (14 mg, 54 %). LC-MS m/z 514 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 2.24 (s, 3 H),

2.78 (s, 6 H), 2.94 (s, 3 H), 3.15 (m, 2 H), 3.55 (m, 2 H), 4.22 (s, 2 H), 7.18 (m, 2 H), 7.56 (m, 2 H), 7.39 (m, 1 H).

Example 115

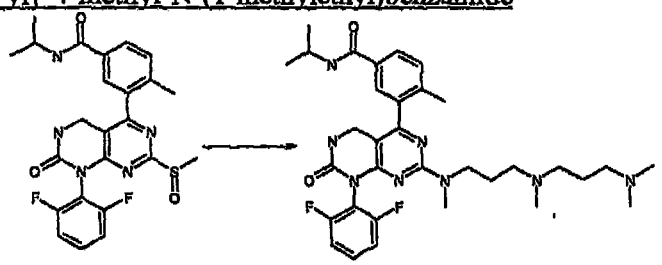
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-*N*-(4-fluorophenyl)-4-methylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-5-fluoro-4-methylbenzoic acid (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) were added 4-flouroaniline (0.025 mL, 0.25 mmol), triethylamine (0.05 mL, 0.36 mmol) and HBTU (20 mg, 0.053 mmol). The reaction mixture was stirred over night. The reaction mixture was concentrated. Separation via a HPLC with TFA followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (26 mg, 88 %). LC-MS m/z 594 $(M+H)^+$; ^{1}H-NMR (MeOD) δ 2.27 (s, 3 H), 2.79 (s, 6 H), 3.16 (m, 2 H), 3.55 (m, 2 H), 4.21 (s, 2 H), 7.15 (m, 4 H), 7.54 (m, 1 H), 7.71 (m, 3 H), 7.85 (m, 1 H).

Example 116

3-{8-(2,6-difluorophenyl)-2-[{3-[[3-(dimethylamino)propyl]-(methyl)amino]propyl}(methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl}-4-methyl-N-(1-methylethyl)benzamide

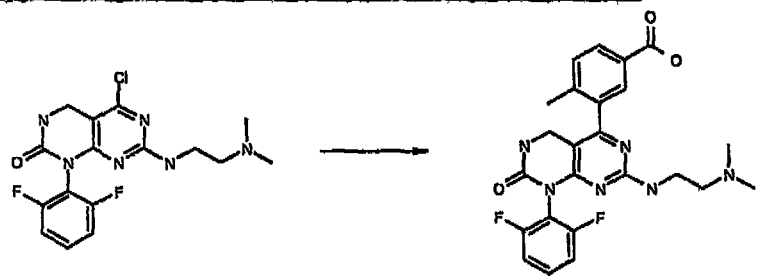


To a solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(1-methylethyl)benzamide (20 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) were added *N*-[3-(dimethylamino)propyl]-

N,N'-dimethyl-1,3-propanediamine (0.004 mL, 0.02 mmol) and triethylamine (0.05 mL, 0.36 mmol). The resultant solution was stirred at room temperature over night. The reaction mixture was concentrated. Separation via a HPLC followed by treatment with t-amino SPE cartridge then provided the title compound as a white solid (7 mg, 29 %). LC-MS m/z 609 $(M + H)^+$; ^{1}H-NMR (MeOD) δ 1.29 (d, 6H), 1.95 (m, 4H), 2.33 (s, 3H), 2.75 (s, 3H), 2.78 (s, 3H), 2.92 (s, 3H), 3.17 (m, 6H), 3.50 (m, 2H), 4.15 (s, 2H), 4.23 (m, 1H), 7.19 (m, 2H), 7.48 (d, 1H), 7.55 (m, 1H), 7.71 (s, 1H), 7.86 (d, 1H).

Example 117

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methylbenzoic acid

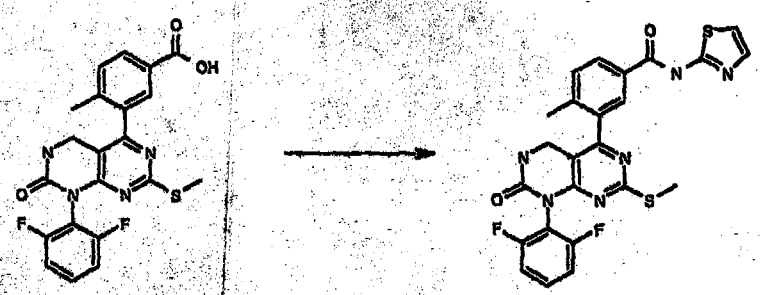


To the solution of 5-chloro-1-(2,6-difluorophenyl)-7-{[2-(dimethylamino)ethyl]amino}-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (191 mg, 0.50 mmol) in dioxane (15 mL) and water (5 mL) were added 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (197 mg, 0.75 mmol), K_2CO_3 (415 mg, 3.0 mmol) and tetrakis(triphenyl-phosphine)palladium(0) (23 mg, 0.025 mmol). The reaction mixture was heated to 150 °C for 15 minutes with microwave. The reaction mixture was concentrated to dry then was added DMSO (2 mL), water (0.5 mL) and HOAc (1 drop). The solution was filtered and applied to the reverse phase HPLC to afford the titled compound 0.24 g (quantitative). LC-MS m/z 483 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.36 (s, 3 H), 2.76 (s, 6H), 3.16 (s, 2 H), 3.56 (s, 2 H), 4.13 (s, 2 H), 7.21 (m, 1 H), 7.53 (m, 2 H), 7.95 (s, 1 H), 8.09 (d, J = 7.6 *Hz*, 1 H).

Example 118

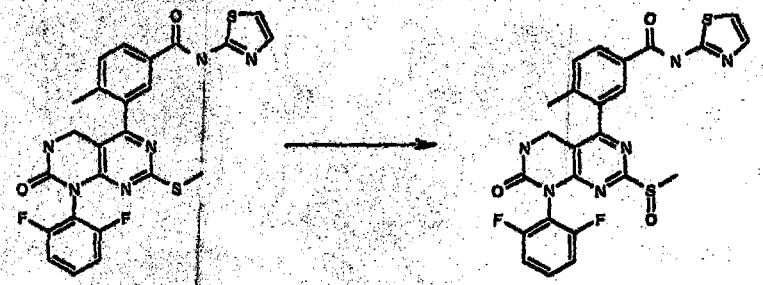
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide

118a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide



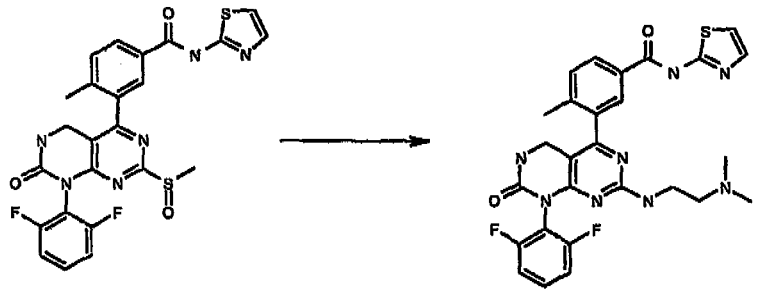
To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methylbenzoic acid (1.41 g, 3.19 mmol) in DMF (50 mL) was added 2-aminothiazole (479 mg, 4.78 mmol), HBTU (1.33 g, 3.51 mmol) and Et_3N (0.90 mL, 6.38 mmol). The reaction mixture was stirred at room temperature for 18 hours before was concentrated and applied to flash chromatography to afford the titled compound 0.99 g (60 %). LC-MS m/z 525 $(M + H)^+$.

118b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide



To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide (262 mg, 0.50 mmol) in dichloromethane (10 mL) was added mCPBA (116 mg, 0.75 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then the reaction mixture was applied to flash chromatography to afford the titled compound 256 mg (95 %). LC-MS m/z 541 $(M + H)^+$.

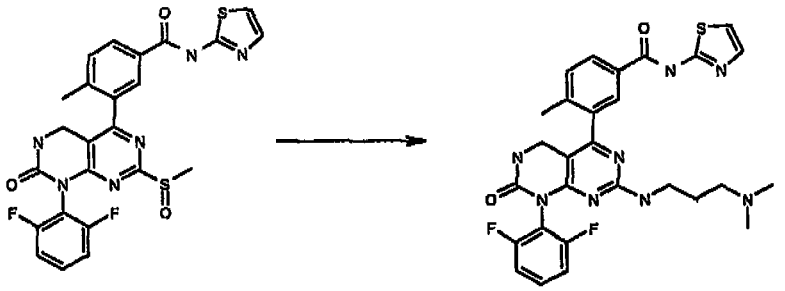
118c) 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



To the solution of 3-[8-(2,6-difluorophenyl)-2-(methylsulfinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide (30 mg, 0.055 mmol) in dichloromethane (3.0 mL) were added *N,N*-dimethyl-1,2-ethanediamine (12.2 µL, 0.11 mmol) and triethylamine (15.6 µL, 0.11 mmol). The reaction mixture was stirred at room temperature for 16 hours then was concentrated, redissolved in DMSO (0.5 mL), filtered and applied to the reverse phase HPLC to afford the titled compound 16.9 mg (54 %). LC-MS m/z 565 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.20 (s, 3 H), 2.33 (m, 7H), 2.81 (s, 2 H), 3.26 (m, 1 H), 4.13 (m, 1 H), 4.43 (s, 1 H), 7.17 (m, 3 H), 7.50 (m, 3 H), 8.01 (m, 2 H).

Example 119

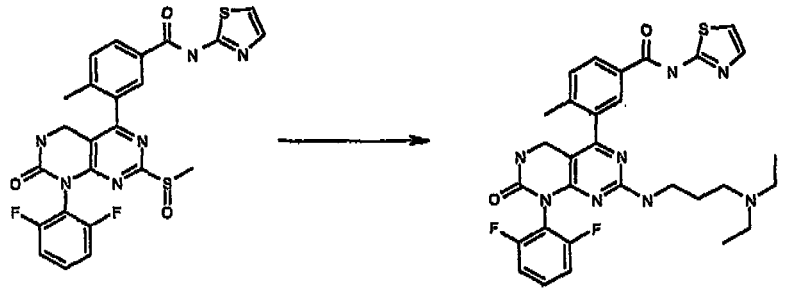
3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N,N,N'*-trimethyl-1,3-propanediamine was used in the displacement (yield: 86%). LC-MS m/z 579 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.83 (m, 2H), 2.37 (s, 3 H), 2.78 (s, 6H), 3.02 (s, br, 2 H), 3.27 (m, 2 H), 4.17 (m, 2 H), 7.19 (m, 3 H), 7.55 (m, 3 H), 7.92 (s, 1 H), 8.08 (m, 1 H).

Example 120

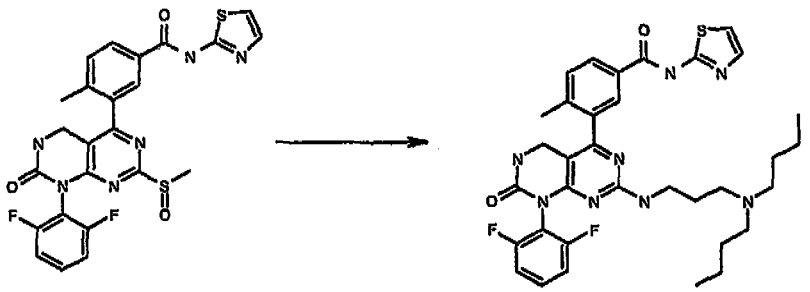
3-[2-{[3-(diethylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N,N*-diethyl-1,3-propanediamine was used in the displacement (yield: 64%). LC-MS m/z 607 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.14 (t, $J = 7.6$ *Hz*, 6 H), 1.70 (m, 2H), 2.34 (s, 3 H), 2.76 (m, 2H), 2.90 (m, 4 H), 3.18 (m, 2 H), 4.11 (m, 2 H), 7.18 (m, 3 H), 7.53 (m, 3 H), 7.89 (s, 1 H), 8.04 (d, $J = 7.2$ *Hz*, 1 H).

Example 121

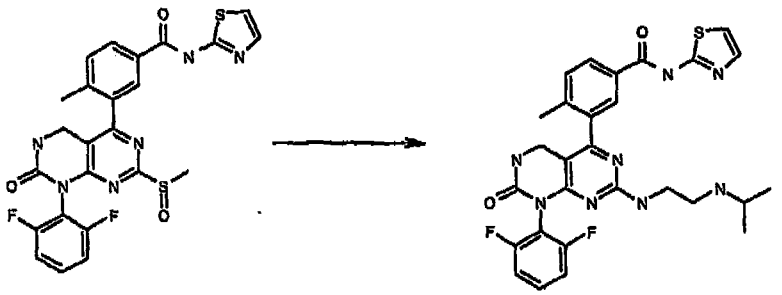
3-[2-{[3-(dibutylamino)propyl]amino}-8-(2,6-difluorophenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N,N*-dibutyl-1,3-propanediamine was used in the displacement (yield: 99%). LC-MS m/z 663 $(M + H)^+$; ^{1}H-NMR (MeOD) 0.97 (m, 6 H), 1.38 (m, 4H), 1.59 (m, 4H), 1.81 (m, 2H), 2.35 (s, 3 H), 3.05 (m, 6H), 3.23 (m, 2 H), 4.11 (m, 2 H), 7.18 (m, 3 H), 7.53 (m, 3 H), 7.89 (s, 1 H), 8.05 (d, $J = 7.6$ *Hz*, 1 H).

Example 122

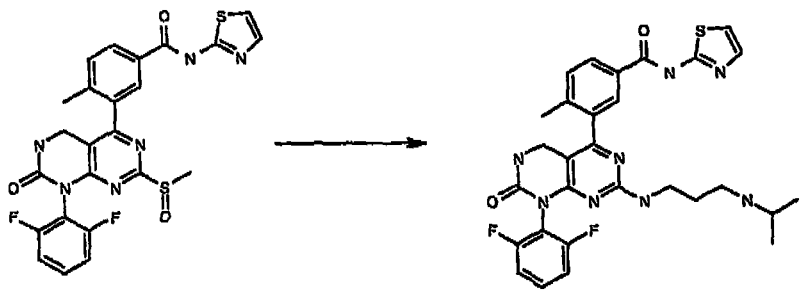
3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N*-(1-methylethyl)-1,2-ethanediamine was used in the displacement (yield: 31%). LC-MS m/z 579 $(M+H)^+$; ^{1}H-NMR (MeOD) 1.16 (d, J = 6.4 *Hz*, 6 H), 2.37 (s, 3 H), 3.02 (s, 2 H), 3.21 (m, 1 H), 3.46 (m, 2 H), 4.19 (m, 2 H), 7.18 (m, 3 H), 7.53 (d, J = 3.6 *Hz*, 2 H), 7.59 (d, J = 8.4 *Hz*, 1 H), 7.92 (s, 1 H), 8.08 (m, 1 H).

Example 123

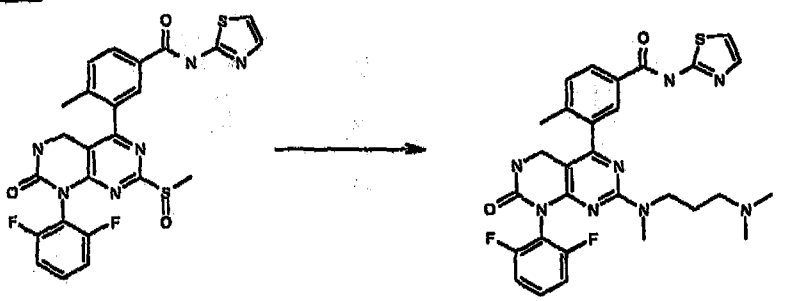
3-[8-(2,6-difluorophenyl)-2-({3-[(1-methylethyl)amino]propyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N*-(1-methylethyl)-1,3-propanediamine was used in the displacement (yield: 71%). LC-MS m/z 593 $(M+H)^+$; ^{1}H-NMR (MeOD) 1.23 (m, 6 H), 1.78 (m, 2 H), 2.36 (s, 3 H), 2.91 (s, 2 H), 3.27 (m, 3 H), 4.15 (m, 2 H), 7.18 (m, 3 H), 7.53 (d, J = 3.6 *Hz*, 2 H), 7.56 (d, J = 8.4 *Hz*, 1 H), 7.91 (s, 1 H), 8.08 (m, 1 H).

Example 124

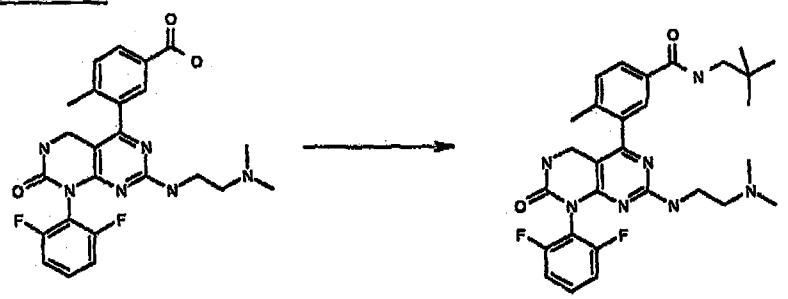
3-{8-(2,6-difluorophenyl)-2-[[3-(dimethylamino)propyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except *N,N,N'*-trimethyl-1,3-propanediamine was used in the displacement (yield: 35%). LC-MS m/z 593 $(M+H)^+$; ^{1}H-NMR (MeOD) 1.62 (m, 2 H), 2.09 (m, 3 H), 2.20 (s, 6 H), 2.36 (s, 3 H), 2.98 (m, 3 H), 3.38 (m, 1 H), 4.17 (m, 2 H), 7.17 (m, 3 H), 7.53 (m, 3 H), 7.92 (s, 1 H), 8.05 (d, $J = 8.0$ *Hz*, 1 H).

Example 125

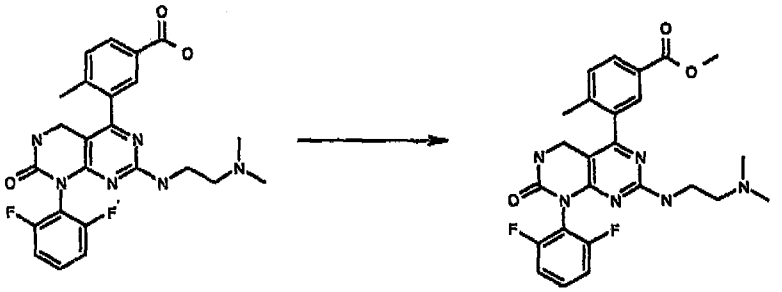
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-(2,2-dimethylpropyl)-4-methylbenzamide



To the solution of 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]-amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl)-4-methylbenzoic acid (30 mg, 0.062 mmol) in dichloromethane (2.0 mL) and DMF (0.5 mL) were added (2,2-dimethylpropyl)amine (10.9 μL, 0.093 mmol), HBTU (25.6 mg, 0.068 mmol) and triethylamine (35.0 μL, 0.25 mmol). The reaction mixture was stirred at room temperature for 16 hours then was applied to HPLC to afford the titled compound 14.9 mg (44%). LC-MS m/z 552 $(M+H)^+$; ^{1}H-NMR (MeOD) 0.99 (s, 9 H), 2.33 (s, 3H), 2.76 (s, 6 H), 3.15 (s, 2 H), 3.24 (s, 2 H), 3.54 (m, 2 H), 4.16 (m, 2 H), 7.18 (m, 2 H), 7.51 (m, 2 H), 7.72 (s, 1 H), 7.89 (m, 1 H).

Example 126

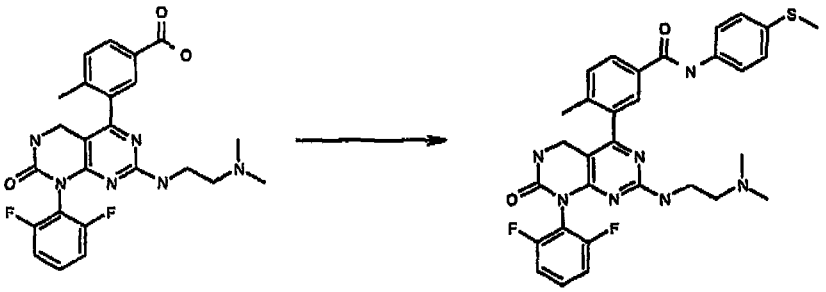
Methyl 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methylbenzoate



The title compound was prepared by following the procedure in Example 125 except methanol was used in the coupling reaction (yield: 44%). LC-MS m/z 497 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.34 (s, 3H), 2.76 (s, 6 H), 3.15 (s, 2 H), 3.54 (m, 2 H), 3.93 (s, 3 H), 4.12 (m, 2 H), 7.18 (m, 2 H), 7.52 (m, 2 H), 7.89 (s, 1 H), 8.04 (m, 1 H).

Example 127

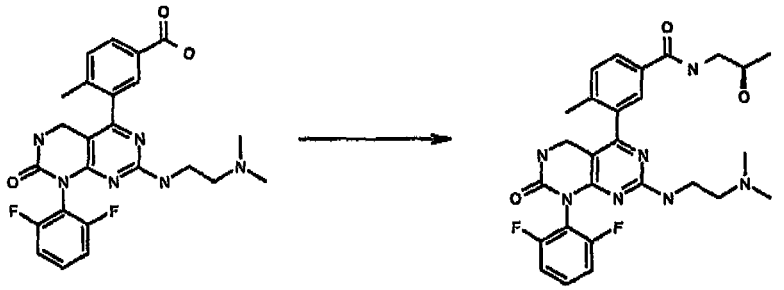
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-[4-(methylthio)phenyl]benzamide



The title compound was prepared by following the procedure in Example 125 except [4-(methylthio)phenyl]amine was used in the coupling reaction (yield: 36%). LC-MS m/z 604 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.24 (s, 6H), 2.35 (s, 3 H), 2.49 (m, 5 H), 3.26 (m, 1 H), 3.37 (m, 1 H), 4.16 (m, 2 H), 7.15 (t, J = 8.4 *Hz*, 2 H), 7.30 (d, J = 8.8 *Hz*, 2 H), 7.53 (m, 2 H), 7.66 (d, J = 8.8 *Hz*, 2 H), 7.82 (s, 1 H), 7.98 (m, 1 H).

Example 128

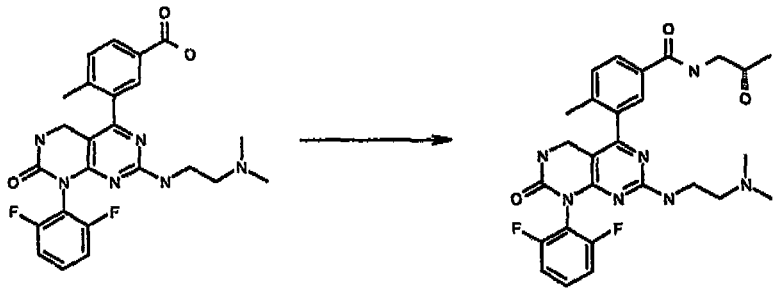
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-[(2*R*)-2-hydroxypropyl]-4-methylbenzamide



The title compound was prepared by following the procedure in Example 125 except (2*R*)-1-amino-2-propanol was used in the coupling reaction (yield: 15%). LC-MS m/z 540 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.22 (d, J = 6.4 *Hz*, 3 H), 2.32 (s, 3 H), 2.51 (m, 6 H), 2.83 (s, 2 H), 3.43 (m, 4 H), 3.97 (m, 1 H), 4.14 (m, 2 H), 7.15 (t, J = 8.4 *Hz*, 2 H), 7.53 (m, 2 H), 7.72 (s, 1 H), 7.88 (m, 1 H).

Example 129

3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*-[(2*S*)-2-hydroxypropyl]-4-methylbenzamide

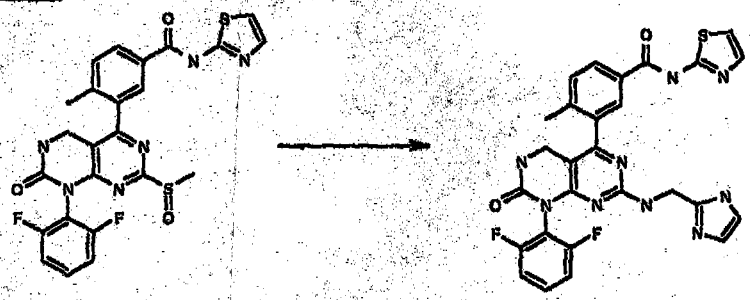


The title compound was prepared by following the procedure in Example 125 except (2*S*)-1-amino-2-propanol was used in the coupling reaction (yield: 37%). LC-MS m/z 540 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.22 (d, J = 6.4 *Hz*, 3 H), 2.32 (s, 3 H), 2.71 (s, 6 H), 3.08 (s, 2 H), 3.43 (m, 4 H), 3.98 (m, 1 H), 4.13 (m, 2 H), 7.17 (t, J = 8.4 *Hz*, 2 H), 7.49 (m, 2 H), 7.72 (s, 1 H), 7.88 (m, 1 H).

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Example 130

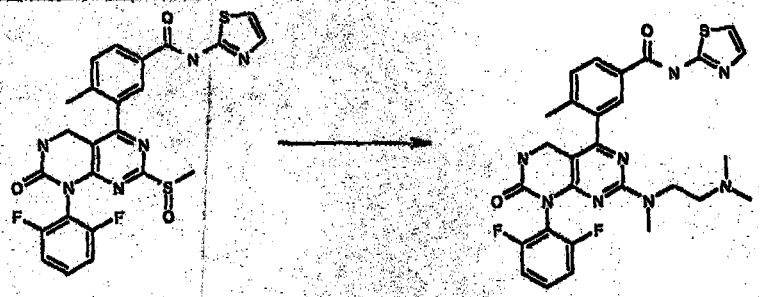
3-{8-(2,6-difluorophenyl)-2-[(1*H*-imidazol-2-ylmethyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 118c except (1*H*-imidazol-2-ylmethyl)amine dihydrochloride was used in the displacement and HPLC with TFA (yield: 18%). LC-MS m/z 574 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.29 (m, 5 H), 4.20 (m, 3 H), 4.57 (m, 3 H), 7.09 (m, 2 H), 7.22 (m, 1 H), 7.48 (m, 5 H), 7.90 (s, 1 H), 8.08 (d, J = 8.0 *Hz*, 1 H).

Example 131

3-{8-(2,6-difluorophenyl)-2-[[2-(dimethylamino)ethyl](methyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate

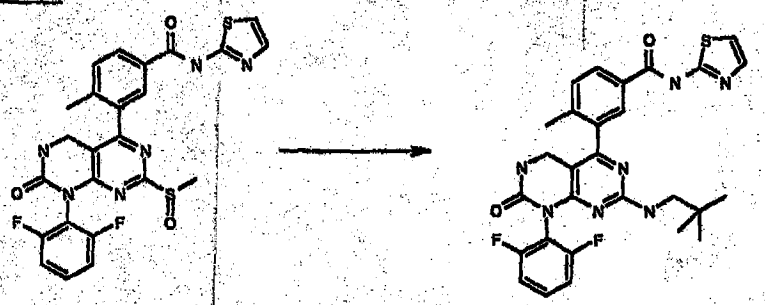


The title compound was prepared by following the procedure in Example 118c except *N*,*N*,*N*'-trimethyl-1,2-ethanediamine was used in the displacement and HPLC with TFA (yield: 49%). LC-MS m/z 579 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.37 (s, 3 H), 2.75 (s, 6 H), 2.97 (s, 3 H), 3.28 (s, 2 H), 3.82 (m, 2 H), 4.23 (m, 2 H), 7.23 (m, 3 H), 7.58 (m, 3 H), 7.94 (s, 1 H), 8.11 (m, 1 H).

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Example 132

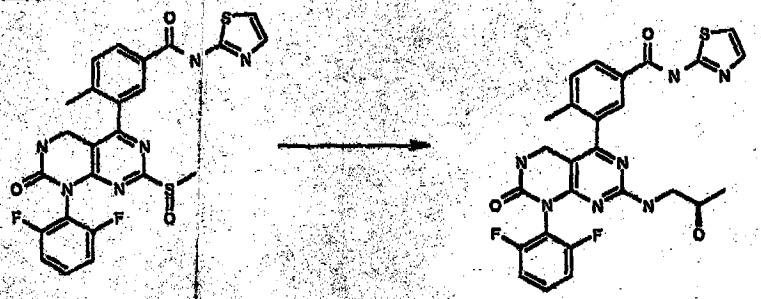
3-{8-(2,6-difluorophenyl)-2-[(2,2-dimethylpropyl)amino]-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl}-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 118c except (2,2-dimethylpropyl)amine was used in the displacement and HPLC with TFA (yield: 32%). LC-MS m/z 564 $(M + H)^+$; ^{1}H-NMR (MeOD) 0.76 (s, 9 H), 2.42 (s, 3 H), 3.00 (s, 2 H), 4.21 (m, 2 H), 7.23 (m, 3 H), 7.55 (d, J = 3.8 *Hz*, 1 H), 7.64 (m, 2 H), 8.07 (s, 1 H), 8.16 (d, J = 8.0 *Hz*, 1 H).

Example 133

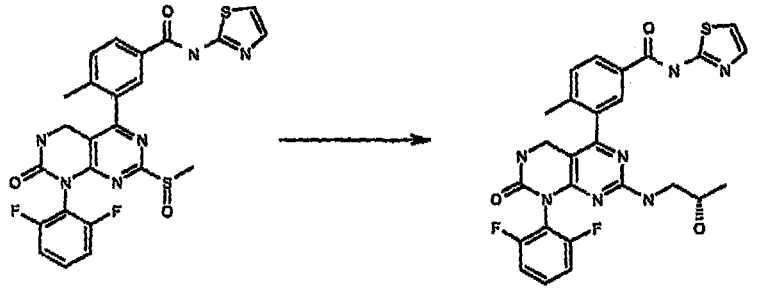
3-(8-(2,6-difluorophenyl)-2-{[(2*R*)-2-hydroxypropyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 118c except (2R)-1-amino-2-propanol was used in the displacement and HPLC with TFA (yield: 49%). LC-MS m/z 552 $(M + H)^+$; ^{1}H-NMR (MeOD) 0.97 (m, 3 H), 2.43 (s, 3 H), 3.00 (s, br, 2 H), 3.19 (s, br, 2 H), 3.76 (m, 1 H), 4.23 (m, 2 H), 7.22 (m, 3 H), 7.56 (m, 2 H), 7.66 (d, J = 8.0 *Hz*, 1 H), 8.06 (s, 1 H), 8.18 (d, J = 8.0 *Hz*, 1 H).

Example 134

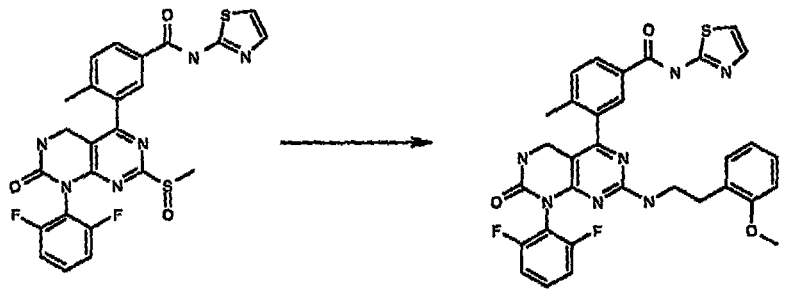
3-(8-(2,6-difluorophenyl)-2-{[(2*S*)-2-hydroxypropyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except (2S)-1-amino-2-propanol was used in the displacement (yield: 27%). LC-MS m/z 552 $(M+H)^+$; ^{1}H-NMR (MeOD) 0.97 (m, 3 H), 2.43 (s, 3 H), 2.99 (s, br, 2 H), 3.18 (s, br, 2 H), 3.76 (m, 1 H), 4.22 (m, 2 H), 7.22 (m, 3 H), 7.55 (m, 2 H), 7.66 (d, J = 8.0 *Hz*, 1 H), 8.05 (s, 1 H), 8.18 (d, J = 7.4 *Hz*, 1 H).

Example 135

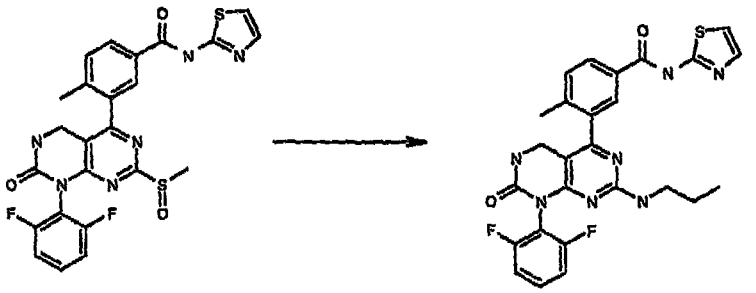
3-[8-(2,6-difluorophenyl)-2-({2-[2-(methyloxy)phenyl]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 118c except 2-[2-(methyloxy)phenyl]ethanamine was used in the displacement and HPLC with TFA (yield: 33%). LC-MS m/z 628 $(M+H)^+$; ^{1}H-NMR (MeOD) 2.38 (s, 3 H), 2.70 (s, br, 2 H), 3.30 (m, 2 H), 3.77 (s, 3 H), 4.16 (m, 2 H), 6.89 (m, 3 H), 7.18 (m, 4 H), 7.57 (m, 3 H), 7.98 (s, 1 H), 8.12 (d, J = 8.0 *Hz*, 1 H).

Example 136

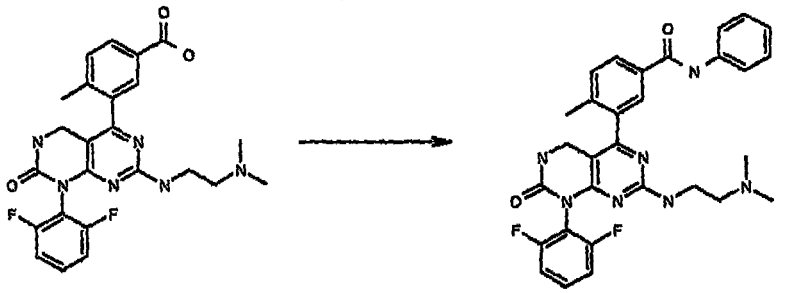
3-[8-(2,6-difluorophenyl)-7-oxo-2-(propylamino)-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-1,3-thiazol-2-ylbenzamide



The title compound was prepared by following the procedure in Example 118c except propyl amine was used in the displacement (yield: 29%). LC-MS m/z 536 $(M + H)^+$; ^{1}H-NMR (MeOD) 0.77 (s, 3 H), 1.45 (m, 2 H), 2.44 (s, 3 H), 3.09 (s, 2 H), 4.23 (m, 2 H), 7.23 (m, 3 H), 7.60 (m, 2 H), 7.68 (m, 1 H), 8.08 (s, 1 H), 8.20 (d, J = 8.0 *Hz*, 1 H).

Example 137

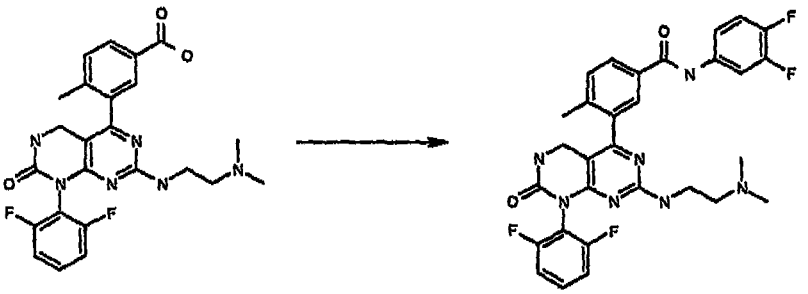
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-phenylbenzamide



The title compound was prepared by following the procedure in Example 125 except aniline was used in the amide coupling reaction (yield: 45%). LC-MS m/z 558 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.36 (s, 3 H), 2.77 (s, 6 H), 3.15 (s, 2 H), 3.55 (m, 2 H), 4.20 (m, 2 H), 7.18 (m, 3 H), 7.38 (m, 2 H), 7.56 (m, 2 H), 7.71 (m, 2 H), 7.84 (s, 1 H), 8.01 (d, J = 8.0 *Hz*, 1 H).

Example 138

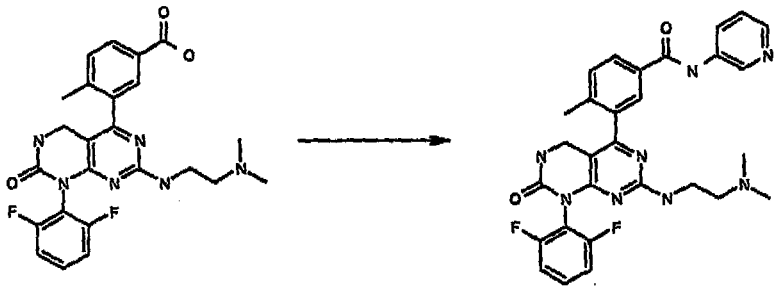
N-(3,4-difluorophenyl)-3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)-ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methylbenzamide



The title compound was prepared by following the procedure in Example 125 except 3,4-difluoro aniline was used in the amide coupling reaction (yield: 15%). LC-MS m/z 594 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.36 (s, 3 H), 2.77 (s, 6 H), 3.16 (s, 2 H), 3.55 (m, 2 H), 4.19 (m, 2 H), 7.24 (m, 3 H), 7.50 (m, 3 H), 7.86 (m, 2 H), 8.00 (m, 1 H).

Example 139

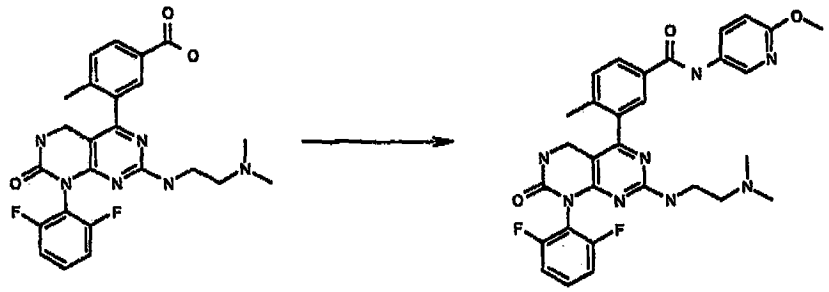
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-3-pyridinylbenzamide



The title compound was prepared by following the procedure in Example 125 except 3-pyridinamine was used in the amide coupling reaction (yield: 6%). LC-MS m/z 559 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.14 (s, 6 H), 2.35 (m, 5 H), 3.24 (m, 2 H), 4.14 (m, 2 H), 7.15 (m, 2 H), 7.50 (m, 3 H), 7.87 (s, 1 H), 8.01 (m, 1 H), 8.30 (m, 2 H), 8.92 (s, 1 H).

Example 140

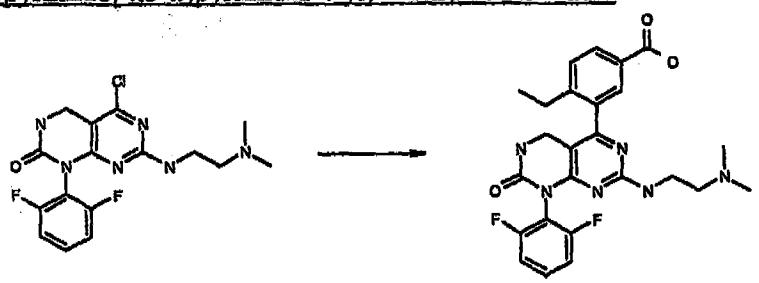
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-[6-(methyloxy)-3-pyridinyl]benzamide



The title compound was prepared by following the procedure in Example 125 except 6-(methyloxy)-3-pyridinamine was used in the amide coupling reaction (yield: 65%). LC-MS m/z 589 $(M + H)^+$; ^{1}H-NMR (MeOD) 2.12 (s, 6 H), 2.33 (m, 5 H), 3.21 (m, 2 H), 3.92 (s, 3 H), 4.11 (m, 2 H), 6.83 (d, J = 8.8 *Hz*, 1 H), 7.14 (m, 2 H), 7.50 (d, J = 8.0 *Hz*, 2 H), 7.82 (s, 1 H), 7.98 (m, 2 H), 8.44 (s, 1 H).

Example 141

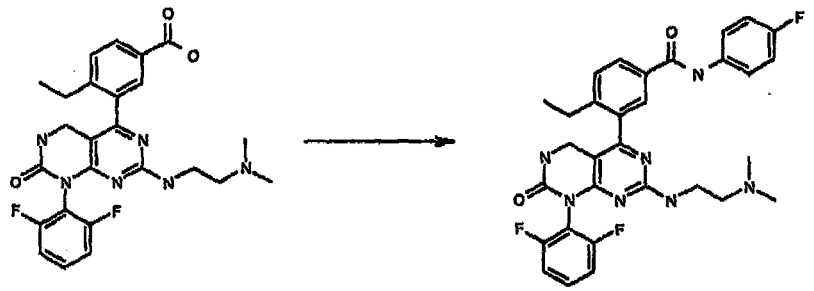
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethylbenzoic acid



The title compound was prepared by following the procedure in Example 117 except 3-(dihydroxyboranyl)-4-ethylbenzoic acid was used in the coupling reaction (yield: 38%). LC-MS m/z 497 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.22 (t, J = 7.6 *Hz*, 3 H), 2.68 (s, 2 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.53 (m, 2 H), 4.13 (m, 2 H), 7.18 (m, 2 H), 7.55 (m, 2 H), 7.86 (s, 1 H), 8.10 (m 1 H).

Example 142

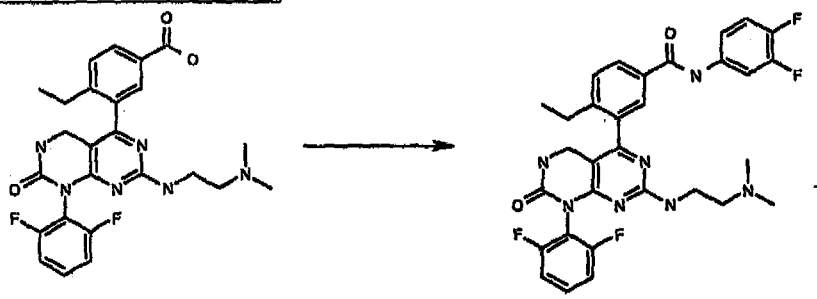
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethyl-*N*-(4-fluorophenyl)benzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 125 except 3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethylbenzoic acid was used as the acid and 4-fluoroaniline was used as the amine for amide coupling and HPLC with TFA (yield: 56%). LC-MS m/z 590 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.22 (t, J = 7.6 *Hz*, 3 H), 2.69 (s, 2 H), 2.77 (s, 6 H), 3.15 (m, 2 H), 3.54 (m, 2 H), 4.13 (m, 2 H), 7.15 (m, 4 H), 7.53 (m, 1 H), 7.60 (d, J = 8.0 *Hz*, 1 H), 7.72 (m, 2 H), 7.80 (s, 1 H), 8.05 (m 1 H).

Example 143

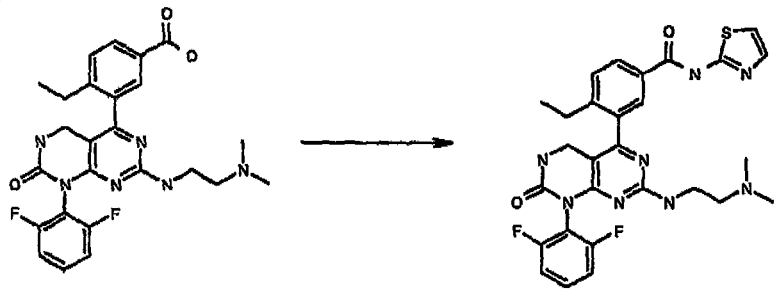
N-(3,4-difluorophenyl)-3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)-ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethylbenzamide trifluoroacetate



The title compound was prepared by following the procedure in Example 142 except 3,4-difluoroaniline was used in the amide coupling reaction and HPLC with TFA (yield: 54%). LC-MS m/z 608 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.24 (t, J = 7.6 *Hz*, 3 H), 2.69 (s, 2 H), 2.77 (s, 6 H), 3.15 (m, 2 H), 3.54 (m, 2 H), 4.18 (m, 2 H), 7.24 (m, 3 H), 7.54 (m, 3 H), 7.85 (m, 2 H), 8.05 (m 1 H).

Example 144

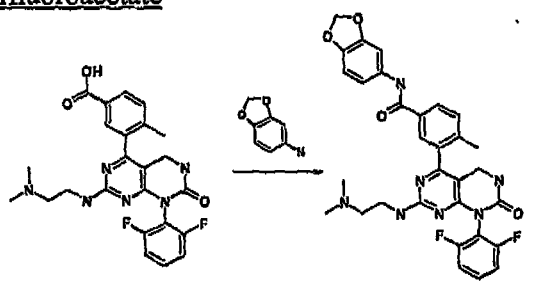
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethyl-*N*-1,3-thiazol-2-ylbenzamide trilfluoroacetate



The title compound was prepared by following the procedure in Example 142 except 1,3-thiazol-2-amine was used in the amide coupling reaction and HPLC with TFA (yield: 43%). LC-MS m/z 579 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.25 (t, J= 7.6 *Hz*, 3 H), 2.71 (s, 2 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.56 (m, 2 H), 4.18 (m, 2 H), 7.20 (m, 3 H), 7.55 (m, 2 H), 7.66 (m, 1 H), 7.90 (s, 1 H), 8.14 (m 1 H).

Example 145

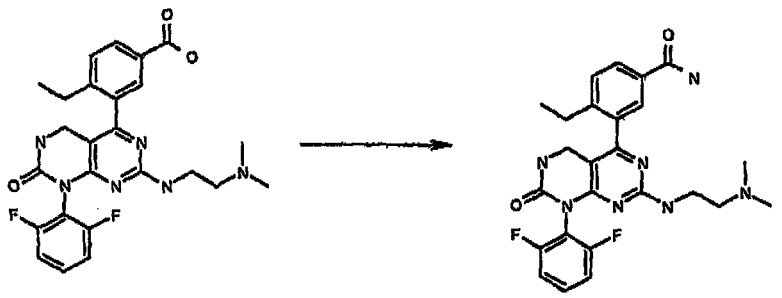
N-1,3-benzodioxol-5-yl-3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)-ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate



Prepared following General Procedure for HATU Couplings. Reversed-phase HPLC (10-90% gradient of acetonitrile in water with 0.1% TFA) provided the title compound 4.9 mg (23 %). LC-MS m/z 602 $(M + H)^+$.

Example 146

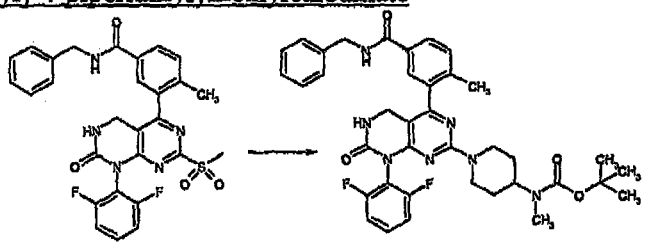
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-ethylbenzamide



The title compound was prepared by following the procedure in Example 142 except ammonia was used in the amide coupling reaction and HPLC without TFA (yield: 64%). LC-MS m/z 496 $(M + H)^+$; ^{1}H-NMR (MeOD) 1.23 (m, 3 H), 2.13 (s, 6 H), 2.35 (m, 2 H), 2.66 (m, 2 H), 3.26 (m, 2 H), 4.12 (m, 2 H), 7.15 (m, 2 H), 7.51 (m, 2 H), 7.73 (s, 1 H), 7.94 (m 1 H).

Example 147

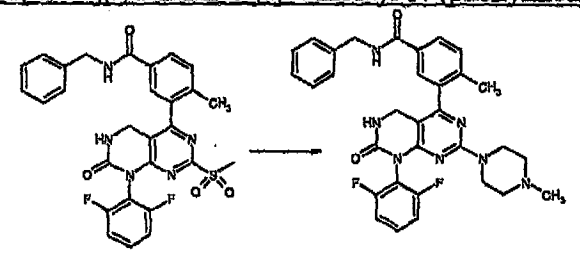
1,1-dimethylethyl {1-[8-(2,6-difluorophenyl)-4-(2-methyl-5-{[(phenylmethyl)amino]carbonyl}phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl]-4-piperidinyl}methylcarbamate



Compound 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.0811g, 0.144 mmol) was dissolved in CH_2Cl_2 (5 mL) and 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (0.0394 g, 0.18 mmol) and triethylamine (0.029 g, 0.288 mmol) were added. The reaction mixture was stirred for 4 days. Additional 1,1-dimethylethyl methyl(4-piperidinyl)carbamate (0.0788 g, 0.36 mmol) and triethylamine (0.058 g, 0.576 mmol) were added and the mixture was stirred under argon at room temperature for an additional 7 days. The solvents were pumped off *in vacuo*, and the residue taken up in EtOAc and washed with 1 N NaOH, brine, dried over anhydrous Na_2SO_4 filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 0-70% EtOAc / hexane. Some impurities remained, so the material was rechromatographed on silica gel (20 g) eluted with 0-50% EtOAc / hexane to give the title compound as a white amorphous solid. mp (dec) 146-150°C. LC-MS m/z 698 $(M+H)^+$, 2.66 min (ret time).

Example 148

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-4-methyl-N-(phenylmethyl)benzamide

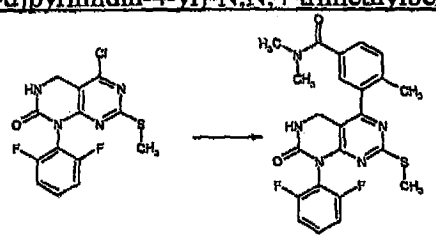


The 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.056g, 0.1 mmol) was dissolved in THF (5 mL) and 1-methylpiperazine (0.0303 g, 0.3 mmol) was added. The reaction was stirred for 72 h. The solvents were pumped off *in vacuo*, and the residue taken up in EtOAc and washed with 1 N NaOH, brine, dried over anhydrous Na_2SO_4 filtered and evaporated. The residue was flash chromatographed on silica gel (20 g) eluted with 6 : 0.1 : 0.01 to 6 : 0.3 : 0.03, CH_2Cl_2 : ethanol : NH_4OH to give the title compound as a white amorphous solid. mp 164-168°C. LC-MS m/z 584 $(M+H)^+$, 1.85 min (ret time).

Example 149

3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide

149a) 3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-N,N,4-trimethylbenzamide

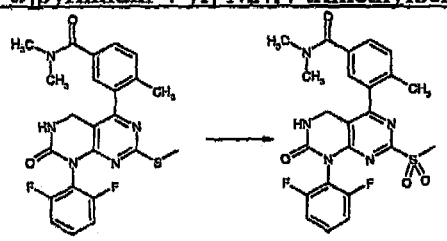


4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (1 g, 3.8 mmoles) was taken up in CH_2Cl_2 (200 mL) and was treated with oxalyl chloride (0.44 mL, 5 mmol) and DMF (1 drop). One hour after gas evolution had ceased, the solvents were pumped off *in vacuo*, and the residue stripped from toluene. This was again taken up in CH_2Cl_2 (200 mL), and excess dimethyl amine was bubbled into the mixture, which was then sealed off and stirred overnight at room temperature. The solvents were pumped off to give the crude *N*,*N*,4-trimethyl-3-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)benzamide, which was used without further purification in the next step.

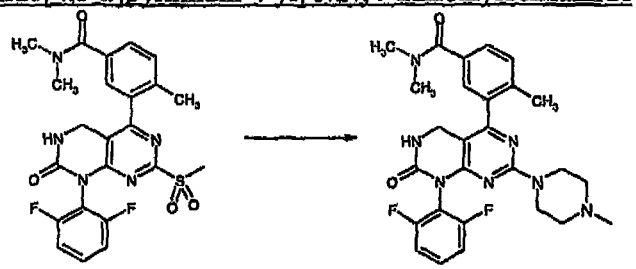
5-chloro-1-(2,6-difluorophenyl)-7-(methylthio)-3,4-dihydropyrimido[4,5-*d*]pyrimidin-2(1*H*)-one (0.102 g, 0.298 mmol), *N*,*N*,4-trimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide from above, (0.129 g, 0.447 mmol), and K_2CO_3 (0.123 g, 0.894 mmol), were taken up in dioxane (6 mL) and water (1.2 mL). The mixture was degassed with argon for 30 min and tetrakis(triphenylphosphine)palladium(0) (0.026 g, 0.022 mmol) was added. The mixture was then heated under argon at 95° C for 18 h. The solvents were pumped off, and after aqueous workup, the crude material was flashed on silica gel (15 g), eluted with a EtOAc / CH_2Cl_2 gradient to give the title compound as a white amorphous solid. mp 144-147°C. LC-MS m/z 470 $(M+H)^+$, 2.02 min (ret time).

149b) 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide



3-[8-(2,6-difluorophenyl)-2-(methylthio)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl]-N,N,4-trimethylbenzamide (0.089 g, 0.19 mmol) was dissolved in CH_2Cl_2 (10 mL) and 50-60% 3-chloroperoxybenzoic acid (0.118 g, 0.38 mmol) was added and the mixture stirred overnight. The solvents were pumped off, and the residue flashed on silica gel eluted with CH_2Cl_2 -90% EtOAc / CH_2Cl_2 to give 3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide. LC-MS m/z 502 $(M+H)^+$, 1.78 min (ret time).

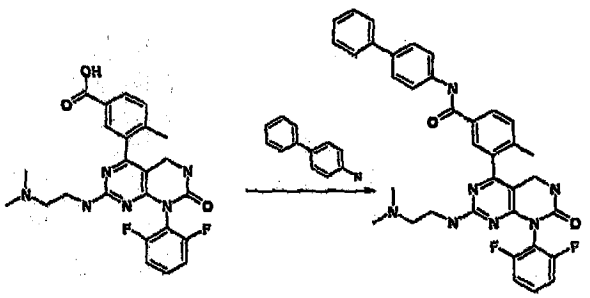
149c) 3-[8-(2,6-difluorophenyl)-2-(4-methyl-1-piperazinyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide



3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide (0.050g, 0.1 mmol) was dissolved in THF (5 mL) and 1-methylpiperazine (0.050 g, 0.5 mmol) was added. The reaction was stirred under argon overnight. The solvents were pumped off *in vacuo*. The residue was flash chromatographed on silica gel (15 g) eluted with CH_2Cl_2 to 6 : 0.5 : 0.05, CH_2Cl_2 : ethanol : NH_4OH to give the title compound as a white amorphous solid. mp 159-162°C. LC-MS m/z 522 $(M+H)^+$, 1.59 min (ret time).

Example 150

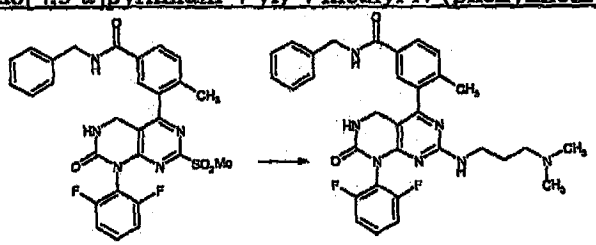
N-4-biphenylyl-3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-d]pyrimidin-4-yl)-4-methylbenzamide trifluoroacetate



Prepared following General Procedure for HATU Couplings. Reversed-phase HPLC (10-90% gradient of acetonitrile in water with 0.1% TFA) provided the title compound 4.4 mg (19 %). LC-MS m/z 634 $(M + H)^+$.

Example 151

3-(8-(2,6-difluorophenyl)-2-{[3-(dimethylamino)propyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-4-methyl-*N*-(phenylmethyl)benzamide

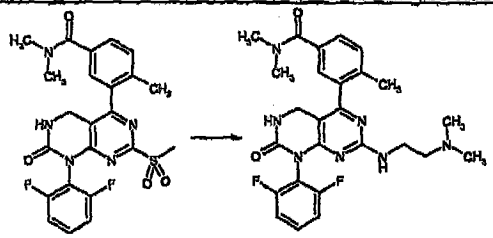


3-[8-(2,6-difluorophenyl)-2-(methylsulfonyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-4-methyl-*N*-(phenylmethyl)benzamide (0.056g, 0.1 mmol) was dissolved in THF (5 mL) and N,N-dimethyl-1,3-propanediamine (0.035 g, 0.3 mmol) was added. The reaction was carried out and

worked up as in Example 148 to give the title compound as a white amorphous solid. mp 141-144°C. LC-MS m/z 586 $(M+H)^+$, 1.52 min (ret time).

Example 152

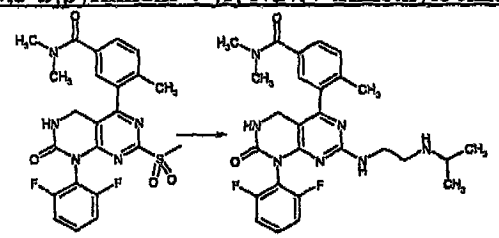
3-(8-(2,6-difluorophenyl)-2-{[2-(dimethylamino)ethyl]amino}-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl)-*N*,*N*,4-trimethylbenzamide



The reaction was carried out and worked up as in Example 149c except substituting dimethylaminoethylamine (0.044g, 0.5 mmol) for 1-methylpiperazine to give the title compound as a white amorphous solid. mp 138-142°C. LC-MS m/z 510 $(M+H)^+$, 1.31 min (ret time).

Example 153

3-[8-(2,6-difluorophenyl)-2-({2-[(1-methylethyl)amino]ethyl}amino)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-4-yl]-*N*,*N*,4-trimethylbenzamide



The reaction was carried out and worked up as in Example 149c except substituting (2-aminoethyl)(1-methylethyl)amine (0.051g, 0.5 mmol) for 1-methylpiperazine to give the title compound as a white amorphous solid. mp 130-133°C. LC-MS m/z 524 $(M+H)^+$, 1.36 min (ret time).

1.65 (m, 2 H) , 2.34 (s, 3 H) , 3.02 (m, 2 H) , 3.17 (m, 4 H) , 3.38 (m, 1 H) , 4.16 (m, 2 H) , 4.23 (m, 1 H) , 7.18 (m, 2 H) , 7.48 (m, 1 H) , 7.54 (m, 1 H) , 7.72 (s, 1 H) , 7.89 (d, 1 H) .

Ejemplo 86

3 - { - 8 - (2,6 - difluorofenil) - 7 - oxo - 2 - [4 - (1 - pirrolidinil) - 1 - piperadinil - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il}N - (4 - fluorofenil) - 4 - metilbenzamida

86a) 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metilsulfonil) - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona

A una solución del compuesto ácido de 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilbenzoico (1.71 g, 5 mmol) en CH2CL2 (60 mL) se agregó m - CPBA (1.17 mg,, 5.2 mmol) . La mezcla se agitó a temperatura ambiente durante 10 minutos, luego se cargo directamente sobre una columna. La cromatografía (EtOAc/Hexano de fase movíl) proporcionó el compuesto del titulo como un solido blanco 1.58 g (88%) . LC - MS m/z 358 $(M + H)^+$.

86b) 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - [4 - (1 - pirrolidinil) - 1 - piperidinil] - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona

A una solución del compuesto del titulo a partir del ejemplo 86[a] (250 mg, 0.70 mmol) en DCM (10 mL) se agregó 4 - (1 - pirrolidin) piperidina (323 mg, 2.1 mmol) y N,N - diisopropiletilamina (0.3 mL,, 1.7 mmol) . La mezcla se agitó a temperatura ambiente durante la noche. La mezcla resultante se concentró. La cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (253 mg, 81%) . LC - MS m/z 449 $(M + H)^+$.

86c) 3 - {8 - (2,6 - difluorofenil) - 7 - oxo - [4 - (1 - pirrolidinil) - 1 - piperidinil] - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida

A una solución del compuesto del titulo a partir del ejemplo 86 b (18 mg, 0.04 mmol) en dioxano (1.5 mL) /agua (0.5 mL) se agregó carbonato de potasio (34 mg, 0.25 mmol) ,tetrakis (trifenilfosfina) paladio (0) (2.3 mg, 0.002 mmol) y N - (4 - fluorofenil) - 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida (22 mg, 0.062 mmol) . La mezcla de reacción se burbujeo con N2 durante 5 minutos, luego se colocó en microondas a 150°C durante 30 minutos. La mezcla resultante se concentró. La cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (14 mg, 54%) . LC - MS m/z 642 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.32 (m, 2 H) , 1.80 (m, 4 H) , 1.88 (m, 2 H) , 2.24 (m, 1 H) , 2.33 (s, 3 H) , 2.62 (m, 4 H) , 2.74 (t, 2 H) , 4.17 (m, 2 H) , 4.40 (m, 2 H) , 7.12 (m, 4 H) , 7.52 (m, 2 H) , 7.72 (m, 2 H) , 7.82 (s, 1 H) , 7.98 (d, 1 H) .

Ejemplo 87

3 - [2 - (1,4 - ` - bipiperidin - 1` - il) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

87a) 7 - (1,4` - bipiperidin - 1` - il) - 5 - cloro - 1 - (2,6 - difluorofenil) - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona

A una solución de 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metilsulfonil) - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona (200 mg, 0.56 mmol) en DCM (10 mL) se agregó 1,4` - bipiperidina (270 mg, 1.61 mmol) y N,N - diisopropiletilamina (0.3 mL,, 1.7 mmol) . La solución resultante se agitó a temperatura ambiente durante la noche. La mezcla resultante se concentró. La cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (298 mg, 83%) . LC - MS m/z 463 $(M + H)^+$.

87b) 3 - [2 - (1,4` - bipiperidin - 1` - il) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetradihidropirimido[4,5 - d]pirimidin - 4il] - N - (4 - fluorofenil) - 4 - metilbenzamida

A una solución de 7 - (1,4` - bipiperidin - 1` -) - 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metilsulfonil) - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona (18 mg, 0.04 mmol) en dioxano (1.5 mL) /agua (0.5 mL) se agregó carbonato de potasio (34 mg, 0.25 mmol) , tetrakis (trifenilfosfina) paladio (0) (2.3 mg, 0.002 mmol) y N - (4 - fluorofenil) - 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida (22 mg, 0.062 mmol) . La mezcla de reacción se burbujeo con N2 durante 5 minutos, luego sometida a microondas a 150°C durante 30 minutos. La mezcla reacción se concentró. La cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del

titulo como un solido blanco (13 mg, 51%) . LC - MS m/z 656 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.37 (m, 2 H) , 1.48 (m, 2 H) , 1.60 (m, 4 H) , 1.80 (m, 2 H) , 2.33 (s, 3 H) , 2.56 (m, 5 H) , 2.72 (t, 2 H) , 4.17 (m, 2 H) , 4.46 (m, 2 H) , 7.12 (m, 4 H) , 7.52 (m, 2 H) , 7.72 (m, 2 H) , 7.82 (s, 1 H) , 7.98 (d, 1 H) .

ejemplo 88

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino}7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (1 - metiletil) benzamida

88a) 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - {[2 - (dimetilamino) etil]amino} - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona

A una solución de 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metilsulfonil) - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona (800 mg, 2.23 mmol) en DCM (45 mL) se agregó N,N - dimetiletilenodiamina (0.36 mL,, 3.23 mmol) y trietilamina (0.63 mL, 4.5 mmol) . La solución resultante se agitó a temperatura ambiente durante la noche. La mezcla resultante se concentró. La cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (730 mg, 85%) . LC - MS m/z 383 $(M + H)^+$.

88b) ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico

A una solución del compuesto del titulo a partir del ejemplo 88 a (100 mg, 0.26 mmol) en dioxano (9 mL) /agua (3mL) se agregó carbonato de potasio (217 mLg, 1.57 mmol), tetrakis (trifenilfosfina) paladio (0) (15 mg, 0.013 mmol) y ácido 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzoico (65 mg, 0.39 mmol). La la mezcla de reacción fue burbujeado con N2 durante 5 minutos. Luego sometido a microondas a 150°C durante 30 minuto. La mezcla resultante se concentró. Luego separación mediante un HPLC proporcionó el compuesto del titulo como un solido blanco (120 mg, 98%). LC - MS m/z 469 $(M + H)^+$.

88c) 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (1 - metiletil) benzamida

A una solución del compuesto del titulo a partir del ejemplo 88 b (23 mg, 0.05 mmol) en CH2Cl2 (3 mL) se agregó isopropilamina (0.005 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) y diisopropil etil amina (0.05 mL, 0.39 mmol). La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL), se secó sobreNA2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (20 mg, 80%). LC - MS m/z 510 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.27 (d, 6 H), 2.16 (s, 6 H), 2.36 (m, 2 H), 3.28 (m, 2 H), 4.23 (m, 1 H), 4.46 (m, 2 H), 7.14 (m, 2 H), 7.49 (m, 1 H), 7.61 (m, 1 H), 7.72 (m, 1 H), 7.96 (d, 1 H), 8.00 (s, 1 H).

Ejemplo 89

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (23 mg, 0.05 mmol) en CH2Cl2 (3 mL) se agregó amoniaco (solución 2.0 M, en isopropanol, 0.0275 mL, 0.055 mmol), HATU (20 mg, 0.052 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol). La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL), se secó sobre NA2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (6 mg, 26%). LC - MS m/z 468 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.16 (s, 6 H), 2.36 (m, 2 H), 3.20 (m, 2 H), 4.46 (s, 2 H), 7.14 (m, 2 H), 7.49 (m, 1 H), 7.61 (m, 1 H), 7.75 (m, 1 H), 8.00 (d, 1 H), 8.07 (s, 1 H).

Ejemplo 90

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N,N - dimetilbenzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (23 mg, 0.05 mmol) en CH2Cl2 (3 mL) se agregó dimetilamina (solución 2.0 M , en THF, 0.0275 mL, 0.055 mmol) , HATU (20 mg, 0.052 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (10 mg, 41%) . LC - MS m/z 496 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.15 (s, 6 H) , 2.36 (m, 2 H) , 3.15 (s, 3 H) , 3.06 (s, 3 H) , 3.23 (m, 2 H) , 4.46 (s, 2 H) , 7.14 (m, 2 H) , 7.12 (m, 1 H) , 7.56 (m, 4 H) .

Ejemplo 91

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - fenilbenzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (23 mg, 0.05 mmol) en CH2Cl2 (3 mL) se agregó anilina (0.005 mL, 0.055 mmol) , HATU (20 mg, 0.052 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (15 mg, 56%) . LC - MS m/z 544 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.43 (s, 6 H) , 2.70 (m, 2 H) , 3.48 (m, 2 H) , 4.52 (s, 2 H) , 7.17 (m, 3 H) , 7.39 (m, 2 H) , 7.52 (m, 1 H) , 7.69 (m, 3 H) , 7.79 (d, 1 H) , 8.08 (d, 1 H) , 8.15 (s, 1 H) .

Ejemplo 92

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 1,3 - tiazol - 2 - ilbenzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó 1,3 - tiazol - 2 - amina (3.5 mg, 0.035 mmol) , HATU (13 mg, 0.034 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movil) proporcionó el compuesto del titulo como un solido blanco (7 mg, 40%) . LC - MS m/z 551 $(M + H)^+$ ^1H - NMR (MeOD) δ 2.22 (s, 6 H) , 2.46 (m, 2 H) , 3.16 (m, 2 H) , 4.51 (s, 2 H) , 7.17 (m, 3 H) , 7.51 (m, 2 H) , 7.69 (m, 1 H) , 7.83 (d, 1 H) , 8.16 (d, 1 H) , 8.23 (s, 1 H) .

Ejemplo 93

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3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) benzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó 4 - fluoroanilina (0.003 mL, 0.035 mmol) , HATU (13 mg, 0.034 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (13 mg, 72%) . LC - MS m/z 562 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.81 (s, 6 H) , 3.21 (m, 2 H) , 3.59 (m, 2 H) , 4.53 (s, 2 H) , 7.17 (m, 4 H) , 7.53 (m, 1 H) , 7.72 (m, 3 H) , 7.80 (d, 1 H) , 8.10 (d, 1 H) , 8.16 (s, 1 H) .

Ejemplo 94

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - metilbenzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó metilamina (solución de M. En THF, 0.018 mL, 0.036 mmol) , HATU (13 mg, 0.034 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (10 mg, 65%) . LC - MS m/z 482 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.16 (s, 6 H) , 2.38 (m, 2 H) , 2.96 (s, 3 H) , 3.22 (m, 2 H) , 4.45 (s, 2 H) , 7.16 (m, 2 H) , 7.50 (m, 1 H) , 7.64 (m, 1 H) , 7.74 (d, 1 H) , 7.95 (d, 1 H) , 8.00 (s, 1 H) .

Ejemplo 95

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - metilbenzamida

A una solución del compuesto del ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó propilamina (0.003 mL, 0.035 mmol) , HATU (13 mg, 0.034 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y agua (5 mL) y se agito. Las capas fueron separadas y la capa organica se lavó con salmuera (8mL) , se secó sobre Na2SO4, se filtró y concentró. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (5 mg, 31%) . LC - MS m/z 510 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.00 (t, 3 H) , 1.67 (m, 2 H) , 2.80 (s, 6 H) , 3.25 (m, 2 H) , 3.40 (m, 2 H) , 3.62 (m, 2 H) ,

4.52 (s, 2 H) , 7.19 (m, 1 H) , 7.53 (m, 1 H) , 7.65 (m, 1 H) , 7.76 (d, 1 H) , 7.98 (d, 1 H) , 8.05 (s, 1 H) .

Ejemplo 96

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 1,3 - tiazol - 2 - ilbenzamida

96a) ácido de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico

A una solución del compuesto 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - {[2 - (dimetilamino) etil] - amino} - 3,4 - dihidropirimido[4,5 - d]pirimidin - 2 (1H) - ona (150 mg, 0.39 mmol) en dioxana (12 mL) /agua (4 mL) se agregó carbonato de potasio (325 mg, 2.36 mmol) , tetrakis (trifenilfosfina) paladio (0) (23 mg, 0.019 mmol) y 4 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzoico (146 mg, 0.59 mmol) . La mezcla de reacción se burbujeo con N2 durante 5 minutos, luego se sometio a microondas a 150°C durante 30 minutos. La mezcla de reacción se concentró. A la mezcla concentrada se agregó DMSO (2mL) , H2O (0.5 mL) y AcOH (0.05 mL) . Luego la separación mediante un HPLC proporcionó el compuesto del titulo como un solido blanco (142 mg, 77%) . LC - MS m/z 469 $(M + H)^+$.

96b) 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 1,3 - tiazol - 2 - ilbenzamida

A una solución del compuesto del titulo del ejemplo 96 a (15 mg, 0.03 mmol) en DMF (3mL) se agregó 1,3 - tiazol - 2 - amina (3.5 mg, 0.035 mmol) , HATU (13 mg, 0.035 mmol) y diisopropiletilamina (0.05 mL, 0.3 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (5 mL) y seagitó. Las capas fueron separadas y la capa organica se lavó con salmuera (8 mL) , se secó sobre Na2SO4, se filtró y evaporó. Luego la cromatografía CombiFlash (DCM/DCM[90]+MeOH[7]+NH4OH[3] de fase movíl) proporcionó el compuesto del titulo como un solido blanco (7 mg, 40%) . LC - MS m/z 551 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.83 (s, 6 H) , 3.15 (m, 2 H) , 3.51 (m, 2 H) , 4.52 (s, 2 H) , 7.17 (m, 3 H) , 7.53 (m, 2 H) , 7.77 (m, 2 H) , 8.19 (m, 2 H) .

Ejemplo 97

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (1 - metiletil) benzamida

A una solución del compuesto ácido de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó isopropilamina (0.0085 mL, 0.1 mmol) y HATU (13 mg, 0.035 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (5 mg, 31%) . LC - MS m/z 510 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.29 (d, 6 H) , 2.79 (s, 6 H) , 3.22 (m, 2 H) , 3.59 (m, 2 H) , 4.26 (m, 1 H) , 4.50 (s, 2 H) , 7.17 (m, 2 H) , 7.54 (m, 1 H) , 7.67 (m, 2 H) , 7.99 (m, 2 H) .

Ejemplo 98

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - propilbenzamida

A una solución del compuesto ácido de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó propilamina (0.0082 mL, 0.1 mmol) y HATU (13 mg, 0.035 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (5 mg, 31%) . LC - MS m/z 510 $(M + H)^+$. ^1H - NMR (MeOD) δ 1.02 (t, 3 H) , 1.68 (m, 2 H) , 2.79 (s, 6 H) , 3.22 (m, 2 H) , 3.59 (m, 2 H) , 4.50 (s, 2 H) , 7.17 (m, 2 H) , 7.54 (m, 1 H) , 7.68 (m, 2 H) , 7.99 (m, 2 H) .

Ejemplo 99

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - fenilbenzamida

A una solución del compuesto ácido de (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó anilina (0.0091 mL, 0.1 mmol) y HATU (13 mg, 0.035 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (7 mg, 40%) . LC - MS m/z 544 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.80 (s, 6 H) , 3.21 (m, 2 H) , 3.59 (m, 2 H) , 4.53 (s, 2 H) , 7.18 (m, 3 H) , 7.40 (m, 2 H) , 7.52 (m, 1 H) , 7.72 (m, 4 H) , 8.12 (m, 2 H) .

Ejemplo 100

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) benzamida

A una solución del compuesto ácido de (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (15 mg, 0.03 mmol) en CH2Cl2 (3 mL) se agregó 4 - fluoroanilina (0.0096 mL, 0.1 mmol) y HATU (13 mg, 0.035 mmol) . La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (7 mg, 39%) . LC - MS m/z 562 $(M + H)^+$. ^1H - NMR (MeOD) δ 2.80 (s, 6 H) , 3.19 (m, 2 H) , 3.59 (m, 2 H) , 4.53 (s, 2 H) , 7.17 (m, 4 H) , 7.52 (m, 1 H) , 7.72 (m, 4 H) , 8.12 (m, 2 H) .

Ejemplo 101

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N,N - dimetilbenzamida

A una solución del compuesto ácido de (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il)

benzoico (20 mg, 0.043 mmol) en CH2Cl2 (2 mL) se agregó dimetilamino (solución de 2.0 M. En THF, 0.0064 mL, 0.13 mmol) y HATU (17.2 mg, 0.045 mmol). La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (18 mg, 85%). LC - MS m/z 496 $(M+H)^+$. ^1H - NMR (MeOD) δ 2.79 (s, 6 H), 3.06 (s, 3 H), 3.16 (s, 3 H), 3.22 (m, 2 H), 3.58 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.54 (m, 1 H), 7.61 (m, 2 H), 7.71 (m, 2 H).

Ejemplo 102

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - metilbenzamida

A una solución del compuesto ácido de (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico (20 mg, 0.043 mmol) en CH2Cl2 (2 mL) se agregó metilamina (solución de 2.0 M. En THF, 0.0064 mL, 0.13 mmol) y HATU (17.2 mg, 0.045 mmol). La mezcla de reacción se agito durante la noche. La mezcla de reacción se concentró. Luego la separación mediante un HPLC con TFA proporcionó el compuesto del titulo como un solido blanco (3 mg, 15%). LC - MS m/z 482 $(M+H)^+$. ^1H - NMR (MeOD) δ 2.79 (s, 6 H), 2.98 (s, 3 H), 3.26 (m, 2 H), 3.59 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.53 (m, 1 H), 7.68 (m, 2 H), 7.99 (m, 2 H).

Ejemplo 103

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) benzamida

A la solución de ácido - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) benzóico (20 mg, 0.043 mmol) en CH_2Cl_2 (2 mL) se agregó amonia (Solución 2.0 M, en propanol, 0.064 mL. 0.13 mmol) y HATU (17.2 mg, 0.045 mmol). La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La separación mediante HPLC con TFA proporcviono el compuesto del titulo como un sólido blanco (18 mg, 90%). LC - MS m/z 468 $(M+H)^+$; ^1H - NMR (MeOD) δ 2.79 (s, 6 H), 3.18 (m, 2 H), 3.58 (m, 2 H), 4.50 (s, 2 H), 7.17 (m, 2 H), 7.53 (m, 1 H), 7.71 (m, 2 H), 8.05 (m, 2 H).

Ejemplo 104

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metil - *N*- (1 - metiletil) benzamida

104a) Ácido 3 - metil - 4 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzóico

A la solución de ácido 4 - yodo - 3 - metilbenzóico (520 mg, 20 mmol) en DMF (8 mL) se agregó acetato de paladio (23 mg, 0.10 mmol), acetato de potasio (590 mg, 6.0 mmol) y 4,4,4',4',5,5,5',5' - octametil - 2,2' - bi - 1,3,2 - dioxaborolano (560 mg, 2.2 mmol). La mezcla de reacción se calentó en un microondas a 150 °C durante 30 minutos. La mezcla de reacción se vertió en agua (25 mL), se extrajo con etilacetato (100 mL) mientras se agregó

ácido acetico (1 mL) . La capa orgánica se lavó con agua (50 mL) , salmuera (50 mL) , se secó sobre sulfato de sodio, se filtró y concentró. El residuo se separó mediante *combiflash* el cual proporcionó el compuesto del titulo como un sólido blanco (460 mg, 88 %) . LC - MS m/z 263 $(M+H)^+$.

104b) Ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico

A una solución de 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - {[2 - (dimetilamino) etil]amino} - 3.4 - dihidropirimido[4,5 - *d*]pirimidin - 2 - (1*H*) - ona (200 mg, 0.52 mmol) en dioxano (15 mL) /agua (5 mL) se agregó carbonato de potasio (433 mg, 3.14 mmol) tetrakis (trifenilfosfina) paladio (0) (31 mg, 0.027 mmol) y ácido 3 - metil - 4 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzóico (205 mg, 0.78 mmol) . L amezcla de reacción se burbujeó con N_2 durante 10 minutos, luego se calentó en un microondas a 150 °C duranrante 30 minutos. La mezcla de reacción se concentró. A la mezcla concentrada se agregó DMSO (2 mL) , H_2O (0.5 mL) y AcOH (0.05 mL) . El Gilson con TFA proporcionó el compuesto del titulo como un sólido blanco (310 mg, 99%) . LC - MS m/z 483 $(M+H)^+$.

104c) Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metil - *N* - (1 - metiletil) benzamida

A la solución del compuesto del titulo del Ejemplo 104b (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó isopropilamina (0.022 mL, 0.25 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La separación mediante HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (17 mg, 63 %) . LC - MS m/z 524 $(M + H)^+$; ^1H - NMR (MeOD) δ 1.29 (d, 6 H) , 2.34 (s, 3 H) , 2.76 (s, 6 H) , 3.16 (m, 2 H) , 3.55 (m, 2 H) , 4.15 (s, 2 H) , 4.25 (m, 1 H) , 7.21 (m, 2 H) , 7.36 (m, 1 H) , 7.55 (m, 1 H) , 7.78 (d, 1 H) , 7.84 (s, 1 H) .

Ejemplo 105

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metil - *N* - propilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó propilamina (0.021 mL, 0.25 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró La separació mediante HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (7 mg, 26%) . LC - MS m/z 524 $(M + H)^+$; ^1H - NMR (MeOD) δ 1.01 (t, 3 H) , 1.67 (m, 2 H) , 2.33 (s, 3 H) , 2.76 (s, 6 H) , 3.16 (m, 2 H) ,

3.55 (m, 2 H) , 4.15 (s, 2 H) , 7.18 (m, 2 H) , 7.36 (m, 1 H) , 7.55 (m, 1 H) , 7.78 (d, 1 H) , 7.84 (s, 1 H) .

Ejemplo 106

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metil - *N* - fenilbenzamida

A una solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - benzóico (25 mg, 0.052 mmol) en CH_2CL_2 (2 mL) se agregó anilina (0.024 mL, 0.25 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La seaparación mediante HPLC con THF proporcionó el compuesto del titulo como un sólido blanco (23 mg, 79%) . LC - MS m/z 558 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.38 (s, 3 H) , 2.77 (s, 6 H) , 3.16 (m, 2 H) , 3.55 (m, 2 H) , 4.17 (s, 2 H) , 7.21 (m, 3 H) , 7.42 (m, 3 H) , 7.55 (m, 1 H) , 7.72 (m, 2 H) , 7.89 (m, 1 H) , 7.97 (s, 1 H) .

Ejemplo 107

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N* - (4 - fluorofenil) - 3 - metilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó 4 - fluoroanilina (0.025 mL, 0.25 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (22 mg, 74%) . LC - MS m/z 576 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.37 (s, 3 H) , 2.77 (s, 6 H) , 3.16 (m, 2 H) , 3.55 (m, 2 H) , 4.17 (s, 2 H) , 7.16 (m, 4 H) , 7.42 (m, 1 H) , 7.55 (m, 1 H) , 7.72 (m, 2 H) , 7.89 (m, 1 H) , 7.97 (s, 1 H) .

Ejemplo 108

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,*N*,3 - trimetilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó dimetilamina (solución de 2.0 M, en THF, 0,13 mL, 0.26 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA proporcionó el compuesto del

titulo como un sólido blanco (19 mg, 72%) . LC - MS m/z 510 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.32 (s, 3 H) , 2.77 (s, 6 H) , 3.06 (s, 3 H) , 3.15 (m, 5 H) , 3.55 (m, 2 H) , 4.17 (s, 2 H) , 7.19 (m, 2 H) , 7.37 (m, 2 H) , 7.46 (s, 1 H) , 7.55 (m, 1 H) .

Ejemplo 109

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,3 - dimetilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó metilamina (solución de 2.0 M, en THF, 0,13 mL, 0.26 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (3 mg, 12%) . LC - MS m/z 496 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.33 (s, 3 H) , 2.76 (s, 6 H) , 2.96 (s, 3 H) , 3.15 (m, 2 H) , 3.55 (m, 2 H) , 4.15 (s, 2 H) , 7.18 (m, 2 H) , 7.36 (m, 1 H) , 7.55 (m, 1 H) , 7.76 (m, 1 H) , 7.83 (s, 1 H) .

Ejemplo 110

Trifluoroacetato de 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 3 - metilbenzóico (25 mg, 0.052 mmol) en CH_2Cl_2 (2 mL) se agregó amoniaco (solución de 2.0 M, en propanol, 0,13 mL, 0.26 mmol) y HBTU (21 mg, 0.055 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (15 mg, 60%) . LC - MS m/z 482 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.33 (s, 3 H) , 2.76 (s, 6 H) , 3.15 (m, 2 H) , 3.55 (m, 2 H) , 4.15 (s, 2 H) , 7.19 (m, 2 H) , 7.36 (m, 1 H) , 7.55 (m, 1 H) , 7.84 (m, 1 H) , 7.91 (s, 1 H) .

Ejemplo 111

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metil - *N* - (1 - metiletil) benzamida

111a) 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metilbenzoato de 1,1 - dimetiletil

A la solución de 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - {[2 - (dimetilamino) etil]amino} - 3,4 - dihidropirimido [4,5 - *d*]pirimidin - 2 - (1*H*) - ona (200 mg, 0.52 mmol) en dioxano (15 mL) /agua (5 mL) se agregó carbonato de potasio (433 mg, 3.14 mmol) tetrakis (trifenilfosfina) paladio (0) (31 mg, 0.027 mmol) y ácido (5 - {[(1,1 - dimetiletil) oxi]carbonil} - 3 - fluoro - 2 - metilfenil) boronico (159 mg, 0.63 mmol) . La mezcla de reacción se burbujeó con N_2 durante 10 minutos, luego se calentó en un microondas a 150 °C durante 30 minutos. La mezcla de reacción se concentró. A la mezcla concentrada se agregó DMSO (2 mL) , H_2O (0.5 mL) y AcOH (0.05 mL) . La separación mediante HPLC proporcionó el compuesto del titulo como un sólido blanco (270 mg, 88%) . LC - MS m/z 587 $(M+H)^+$.

111b) Ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metilbenzóico

A la solución del compuesto del titulo del ejemplo 111a (260 mg, 0.45 mmol) en CH_2Cl_2 (1 mL) se agregó TFA (0.045 mmol, 5.84 mmol) y trietilsilano (0.18 mL, 1.12 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La separación mediante una HPLC proporcionó el compuesto del titulo como un sólido blanco (260 mg, 96%) . LC - MS m/z 501 $(M+H)^+$.

111c) 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metil - *N* - (1 - metiletil) benzamida

A la solución del compuesto del titulo del ejemplo 111b (25 mg, 0.05 mmol) en CH_2Cl_2 (2 mL) se agregó isopropilamina (0.021 mmol, 0.25 mmol) y HBTU (0.18 mL, 1.12 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La separación mediante una HPLC con TFA proporcionó el compuesto del titulo como un sólido blanco (9 mg, 33%) . LC - MS m/z 542 $(M + H)^+$; ^1H - NMR (MeOD) δ 1.27 (d, 6 H) , 2.40 (s, 3 H) , 2.78 (s, 6 H) , 3.15 (m, 2 H) , 3.55 (m, 2 H) , 4.22 (m, 3 H) , 7.18 (m, 2 H) , 7.57 (m, 2 H) , 7.71 (m, 1 H) .

Ejemplo 112

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metil - *N* - fenilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metilbenzóico (25 mg, 0.05 mmol) en CH_2Cl_2 (2 mL) se agregó anilina (0,025 mL, 0.25 mmol) y HBTU (20 mg, 0.053 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA seguida por tratamient0 con cartucho t - amino SPE proporcionó el compuesto del titulo como un sólido blanco (10 mg, 35%) . LC - MS m/z 576 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.27 (s, 3 H) , 2.79 (s, 6 H) , 3.15 (m, 2 H) , 3.55 (m, 2 H) , 4.21 (s, 2 H) , 7.19 (m, 3 H) , 7.39 (m, 2 H) , 7.54 (m, 1 H) , 7.71 (m, 3 H) , 7.86 (m, 1 H) .

Ejemplo 113

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,*N*,4 - trimetilbenzamida

A la solución de ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metilbenzóico (25 mg, 0.05 mmol) en CH_2Cl_2 (2 mL) se agregó dimetilamina (solución de 2.0 M, en THF,013 mL, 0.26 mmol) trietilamina (0.05 mL) y HBTU (20 mg, 0.053 mmol) . La mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA seguida por tratamiento con cartucho t - amino SPE proporcionó el compuesto del titulo como un sólido blanco (15 mg, 57%) . LC - MS m/z 528 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.23 (s, 3 H) , 2.78 (s, 6 H) , 3.06 (s, 3 H) , 3.15 (m, 5 H) , 3.55 (m, 2 H) , 4.22 (s, 2 H) , 7.19 (m, 3 H) , 7.34 (m, 1 H) , 7.56 (m, 1 H) .

Ejemplo 114

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,4 - dimetilbenzamida

A la solución de ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - 4 - metilbenzóico (25 mg, 0.05 mmol) en CH_2Cl_2 (2 mL) se agregó metilamina (solución de 2.0 M, en THF,013 mL, 0.26 mmol) trietilamina (0.05 mmol) y HBTU (20 mg, 0.053 mmol) . La

mezcla de reacción se agitó durante la noche. La separación mediante HPLC con TFA seguida por tratamiento con cartucho t - amino SPE proporcionó el compuesto del titulo como un sólido blanco (14 mg, 54%) . LC - MS m/z 514 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.24 (s, 3 H) , 2.78 (s, 6 H) , 2.94 (s, 3 H) , 3.15 (m, 2 H) , 3.55 (m, 2 H) , 4.22 (s, 2 H) , 7.18 (m, 2 H) , 7.56 (m, 2 H) , 7.39 (m, 1 H) .

Ejemplo 115

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - N - (4 - fluorofenil) - 4 - metilbenzamida

A una solución de ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 5 - fluoro - N - (4 - fluorofenil) - 4 - metilbenzóico (25 mg, 0.05 mmol) en CH_2Cl_2 (2 ml) se agregó 4 - flouroanilina (0.025 mL, 0.25 mmol) , trietilamina (0.05 mL, 0.36 mmol) y HBTU (20 mg, 0.053 mmol) . La mezcla de reacción se agitó durante la noche. La mezcla de reacción se concentró. La separación mediante una HPLC con TFA seguido por un tratamiento con cartucho t - amino SPE proporcionó el compuesto del titulo como un sólido (26 mg, 88 %) . LC - MS m/z 594 $(M + H)^+$; ^1H - NMR (MeOD) δ 2.27 (s, 3 H) , 2.79 (s, 6 H) , 3.16 (m, 2 H) , 3.55 (m, 2 H) , 4.21 (s, 2 H) , 7.15 (m, 4 H) , 7.54 (m, 1 H) , 7.71 (m, 3 H) , 7.85 (m, 1 H) .

Ejemplo 116

3 - {8 - (2,6 - difluorofenil) - 2 - [{3 - [[3 - (dimetilamino) propil] - (metil) amino]propil} (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (1 - metiletil) benzamida

A una solución de 3 - {8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (1 - metiletil) benzamida (20 mg, 0.04 mmol) en CH_2Cl_2 (1 mL) se agregó *N* - [3 - (dimetilamino) propil] - *N,N'* - dimetil - 1,3 - propanediamina (0.004 mL, 0.02 mmol) y trietilamina (0.05 mL, 0.36 mmol) . La solución resultante se agitó a temperatura ambiente durante la noche. La mezclad e reacción se concentró. La separación mediante una HPLC seguida por tratamiento con cartucho t - amino SPE proporcionó el compuesto del titulo com oun sólido blanco (7 mg, 29%) . LC - MS m/z 609 $(M + H)^+$; ^1H - NMR (MeOD) δ 1.29 (d, 6H) , 1.95 (m, 4H) , 2.33 (s, 3H) , 2.78

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500

(s, 3H) , 2.92 (s, 3H) , 3.17 (m, 6H) , 3.50 (m, 2H) , 4.15 (s, 2H) , 4.23 (m, 1H) , 7.19 (m, 2H) , 7.48 (d, 1H) , 7.55 (m, 1H) , 7.71 (s, 1H) , 7.86 (d, 1H) .

Ejemplo 117

Ácido 3 - {8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzóico

A la solución de 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - {[2 - (dimetilamino) etil]amino} - 3,4 - dihidropirimido[4,5 - d*pirimidin - 2 (1H) - ona (191 mg, 0.50 mmol) en dioxano (15 mL) se agregó ácido 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzóico (197 mg, 0.75 mmol) , K_2CO_3 (415 mg, 3.0 mmol) y tetrakis (trifenilfosfina) paladio (0) (23 mg, 0.025 mmol) . La mezcla de reacción se calentó a 150 °C durante 15 minutos con microondas. La mezcla de reacción se concentró para secar luego se agregó DMSO (2 mL) , agua (0.5 mL) y HOAc (1 gota) . La solución se filtró y se aplicó a la HPLC de fase inversa para proporcionar el compuesto del título 0.24 g (cuantitativo) . LC - MS m/z 483 $(M + H)^+$; ^1H - NMR (MeOD) 2.36 (s, 3 H) , 2.76 (s, 6H) , 3.16 (s, 2H) , 3.56 (s, 2H) , 4.13 (s, 2H) , 7.21 (m, 1 H) , 7.53 (m, 2 H) , 7.95 (s, 1 H) , 8.09 (d, $J = 7.6$ *Hz*, 1 H) .

Ejemplo 118

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

118a) 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

A una solución de ácido 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilbenzóico (1.41 g, 3.51 mmol) en DMF (50 mL) se agregó 2 - aminotiazola (479 mg, 4.78 mmol) , HBTU (1,33 g, 3.51 mmol) y Et_3N (0.90 mL, 6.38 mmol) . La mezcla de reacción se agitó a temperatura ambiente durante la 18 horas antes de ser concentrado y aplicado a cromatografía rápida para proporcionar el compuesto del título 0.99 g (60%) . LC - MS m/z 525 $(M + H)^+$.

118b) 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

A la solución de 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida (262 mg, 0.50 mmol) en diclorometano (10 mL) se agregó mCPBA (116 mg, 0.75 mmol) . La mezcla de reacción se agitó a temperatura ambiente durante 10 minutos. Luego la mezcla de reacción se aplicó a cromatografía rápida para proporcionar el compuesto del titulo 256 mg (95 %) . LC - MS m/z 541 $(M + H)^+$.

118c) 3 - [8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

A la solución de3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahi0dropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida (30 mg, 0.055 mmol) en diclorometano (3.0 mL) se agregó *N,N* - dimetil - 1,2 - etanediamina (12.2 µL, 0.11 mmol) y trietilamina (15.6 µL, 0.11 mmol) . La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se concentró, redisolvió en DMSO (0.5 mL) , filtró y aplicó a la HPLC de fase inversa para proporcionar el compuesto del titulo 16.9 mg (54 %) . LC - MS m/z 565 $(M + H)^+$; ^{1}H - NMR (MeOD) 2.20 (s, 3 H) , 2.33 (m, 7H) , 2.81 (s, 2H) , 3.26 (m, 1 H) , 4.13 (m, 1 H) , 4.43 (s, 1H) , 7.17 (m, 3 H) , 7.50 (m, 3 H) , 8.01 (m, 2H) .

Ejemplo 119

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (dimetilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó *N,N,N'* - trimetil - 1,3 - propanediamina en el desplazamiento. (rendimiento: 86%) . LC - MS m/z 579 $(M + H)^+$; ^{1}H - NMR (MeOD) 1.83 (m, 2H) , 2.37 (s, 3H) , 2.78 (s, 6H) , 3.02 (s, br, 2 H) , 3.27 (m , 2H) , 4.17 (m, 2 H) , 7.19 (m, 3 H) , 7.55 (m, 3 H) , 7.92 (s, 1 H) , 8.08 (m, 1H) .

Ejemplo 120

3 - [2 - {[3 - (dimetilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el Ejemplo 118c excepto que se utilizó *N,N* - dietil - 1,3 - propanediamina en el desplazamiento (rendimiento: 64%). LC - MS m/z 607 $(M + H)^+$; ^1H - NMR (MeOD) 1.14 (t, $J = 7.6$ *Hz*, 6 H), 1.70 (m, 2H), 2.34 (s, 3 H), 2.76 (m, 2H), 2.90 (m, 4H), 3.18 (m, 2H), 4.11 (m, 2 H), 7.18 (m, 3 H), 7.53 (m, 3 H), 7.89 (s, 1H), 8.04 (d, $J = 7.2$ *Hz*, 1 H).

Ejemplo 121

3 - [2 - {[3 - (dibutilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el Ejemplo 118c excepto que se utilizó *N,N* - butil - 1,3 - propanediamina en el desplazamiento (rendimiento: 99%). LC - MS m/z 663 $(M + H)^+$; ^1H - NMR (MeOD) 0.97 (m, 6H), 1.38 (m, 4H), 1.59 (m, 4 H), 1.81 (m, 2H), 2.35 (s, 3 H), 3.05 (m, 6H), 3.23 (m, 2 H), 4.11 (m, 2 H), 7.18 (m, 3 H), 7.53 (m, 3 H), 7.89 (s, 1H), 8.05 (d, $J = 7.6$ *Hz*, 1 H).

Ejemplo 122

3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - [(1 - metiletil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el Ejemplo 118c excepto que se utilizó *N* - (1 - metiletil) - 1,2 - etanediamina en el desplazamiento (rendimiento: 31%). LC - MS m/z 579 $(M + H)^+$; ^1H - NMR (MeOD) 1.16 (d, $J = 6.4$ *Hz*, 6 H), 2.37 (s, 3 H), 3.02 (s, 2 H), 3.21 (m, 1 H), 3.46 (m, 2H), 4.19 (m, 2 H), 7.18 (m, 3 H), 7.53 (d, $J = 3.6$ *Hz*, 2 H). 7.59 (d, $J = 8.4$ *Hz*, 1 H), 7.92 (s, 1 H), 8.08 (m, 1H).

Ejemplo 123

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1 - metiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el Ejemplo 118c excepto que se utilizó *N* - (1 - metiletil) - 1,3 - propanediamina en el desplazamiento (rendimiento: 71%). LC - MS m/z 593 $(M + H)^+$; ^1H - NMR (MeOD) 1.23 (m, 6 H), 1.78 (m, 2 H), 2.36 (s, 3 H), 2.91 (s, 2 H), 3.27 (m, 3 H), 4.15 (m, 2 H), 7.18 (m, 3H), 7.53 (d, $J = 3.6$ *Hz*, 2 H), 7.56 (d, $J = 8.4$ *Hz*, 1 H), 7.91 (s, 1 H), 8.08 (m, 1H).

Ejemplo 124

3 - [8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el Ejemplo 118c excepto que se utilizó *N,N,N'* - trimetil - 1,3 - propanediamina en el desplazamiento (rendimiento: 35%). LC - MS m/z 593 $(M + H)^+$; ^1H - NMR (MeOD) 1.62 (m, 2 H), 2.09 (m, 3 H), 2.20 (s, 6 H), 2.36 (s, 3 H), 2.98 (m, 3 H), 3.38 (m, 1 H), 4.17 (m, 2 H), 7.17 (m, 3H), 7.53 (m, 3 H), 7.92 (s, 1H), 8.05 (d, $J = 8.0$ *Hz*, 1 H).

Ejemplo 125

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N* - (2,2 - dimetilpropil) - 4 - metilbenzamida

A una solución de ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil] - amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metilbenzóico (30 mg, 0.062 mmol) en diclorometano (2.0 mL) y DMF (0.5 mL) se agregó (2,2 -

dimetilpropil) amina (10.9 µL, 0.093 mmol) , HBTU (25,6 mg, 0.068 mmol) y trietilamina (35.0 µL, 0.25 mmol) . La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y luego se aplico a una HPLC para proporcionar el compuesto del titulo 14.9 mg (44%) . LC - MS m/z 552 $(M + H)^+$; ^1H - NMR (MeOD) 0.99 (s, 9 H) , 2.33 (s, 3 H) , 2.76 (s, 6 H) , 3.15 (s, 2 H) , 3.24 (s, 2H) , 3.54 (m, 2 H) , 4.16 (m, 2 H) , 7.18 (m, 2 H) . 7.51 (m, 2H) , 7.72 (s, 1H) , 7.89 (m, 1H) .

Ejemplo 126

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzoato de metilo

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó metanol en la reacción de acoplamiento (rendimiento: 44%) . LC - MS m/z 497 $(M + H)^+$; ^1H - NMR (MeOD) 2.34 (s, 3 H) , 2.76 (s, 6 H) , 3.15 (s, 2 H) , 3.54 (m, 2 H) , 3.93 (s, 3 H) , 4.12 (m, 2 H) , 7.18 (m, 2 H) , 7.52 (m, 2 H) . 7.89 (s, 1H) , 8.04 (m, 1 H) .

Ejemplo 127

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - [4 - (metiltio) fenil]benzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó [4 - (metiltio) fenil]amina en la reacción de acoplamiento (rendimiento: 36%) . LC - MS m/z 604 $(M + H)^+$; ^1H - NMR (MeOD) 2.24 (s, 6H) , 2.35 (s, 3 H) , 2.49 (m, 5 H) , 3.26 (m, 1 H) , 3.37 (m, 1 H) , 4.16 (m, 2 H) , 7.15 (t, $J = 8.4$ *Hz*, 2 H) , 7.30 (d, $J = 8.8$ *Hz*, 2 H) , 7.53 (m, 2 H) , 7.66 (d, $J = 8.8$ *Hz*, 2 H) , 7.82 (s, 1H) , 7.98 (m, 1 H) .

Ejemplo 128

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N* - [4 - (2R) - 2 - hidroxipropil] - 4 - metilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó (2R) - 1 - amino - 2 - propanol en la reacción de acoplamiento (rendimiento: 15%) . LC - MS m/z 540 $(M + H)^+$; ^1H - NMR (MeOD) 1.22 (d, $J = 6.4$ *Hz*, 3 H) , 2.32 (s, 3H) , 2.51 (m, 6 H) , 2.83 (s, 2 H) , 3.43 (m, 4 H) , 3.97 (m, 1 H) , 4.14 (m, 2 H) , 7.15 (t, $J =$ 8.4 *Hz*, 2 H) , 7.53 (m, 2 H) , 7.72 (s, 1 H) , 7.88 (m, 1 H) .

Ejemplo 129

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N* - [(2S) - 2 - hidroxipropil] - 4 - metilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó (2S) - 1 - amino - 2 - propanol en la reacción de acoplamiento (rendimiento: 37%) . LC - MS m/z 540 $(M + H)^+$; ^1H - NMR (MeOD) 1.22 (d, $J = 6.4$ *Hz*, 3 H) , 2.32 (s, 3H) , 2.71 (s, 6 H) , 3.08 (s, 2 H) , 3.43 (m, 4 H) , 3.98 (m, 1 H) , 4.13 (m, 2 H) , 7.17 (t, $J =$ 8.4 *Hz*, 2 H) , 7.49 (m, 2 H) , 7.72 (s, 1 H) , 7.88 (m, 1 H) .

Ejemplo 130

Trifluoroacetato de 3 - {8 - (2,6 - difluorofenil) - 2 - [(1*H* - imidazol - 2 - ilmetil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó dihidrocloruro de (1H - imidazol - 2 - ilmetil) amina en el desplazamiento y HPLC con TFA (rendimiento: 18%) . LC - MS m/z 574 $(M + H)^+$; ^1H - NMR (MeOD) 2.29

(m, 5H) , 4.20 (m, 3 H) , 4.57 (m, 3 H) , 7.09 (m, 2 H) , 7.22 (m, 1 H) , 7.48 (m, 5 H) , 7.90 (s, 1H) , 8.08 (d, J = 8.0 *Hz*, 1 H) .

Ejemplo 131

Trifluoroacetato de 3 - {8 - (2,6 - difluorofenil) - 2 - [[2 - (dimetilamino) etil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó *N,N,N'* - trimetil - 1,2 - etanediamina en el desplazamiento y HPLC con TFA (rendimiento: 49%) . LC - MS m/z 579 $(M + H)^+$; ^{1}H - NMR (MeOD) 2.37 (s, 3 H) , 2.75 (s, 6 H) , 2.97 (s, 3 H) , 3.28 (s, 2 H) , 3.82 (m, 2 H) , 4.23 (m, 2 H) , 7.23 (m, 3 H) , 7.58 (m, 3 H) , 7.94 (s, 1H) , 8.11 (m, 1 H) .

Ejemplo 132

Trifluoroacetato de 3 - {8 - (2,6 - difluorofenil) - 2 - [(2,2 - dimetilpropil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó (2,2 - dimetilpropilamina) en el desplazamiento y HPLC con TFA (rendimiento: 32%) . LC - MS m/z 564 $(M + H)^+$; ^{1}H - NMR (MeOD) 0.76 (s, 9 H) , 2.42 (s, 3 H) , 3.00 (s, 2 H) , 4.21 (m, 2 H) , 7.23 (m, 3 H) , 7.55 (d, J = 3.8 *Hz*, 1 H) , 7.64 (m, 2H) , 8.07 (s, 1H) , 8.16 (d, J = 8.0 *Hz*, 1 H) .

Ejemplo 133

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[(2R) - 2 - hidroxipropil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó (2R) - 1 - amino - 2 - propanol en el desplazamiento y HPLC con TFA (rendimiento: 49%) . LC - MS m/z 552 $(M+H)^+$; ^1H - NMR (MeOD) 0.97 (m, 3 H) , 2.43 (s, 3 H) , 3.00 (s, br, 2 H) , 3.19 (s, br, 2H) , 3.76 (m, 1 H) , 4.23 (m, 2 H) , 7.22 (m, 3H) , 7.56 (m, 2H) , 7.66 (d, J = 8.0 *Hz*, 1 H) , 8.06 (s, 1H) , 8.18 (d, J = 8.0 *Hz*, 1 H) .

Ejemplo 134

3 - {8 - (2,6 - difluorofenil) - {[(2S) - 2 - hidroxipropil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó (2SS) - 1 - amino - 2 - propanol en el desplazamiento y HPLC con TFA (rendimiento: 49%) . LC - MS m/z 552 $(M+H)^+$; ^1H - NMR (MeOD) 0.97 (m, 3 H) , 2.43 (s, 3 H) , 2.99 (s, br, 2 H) , 3.18 (s, br, 2H) , 3.76 (m, 1 H) , 4.22 (m, 2 H) , 7.22 (m, 3 H) , 7.55 (m, 2H) , 7.66 (d, J = 8.0 *Hz*, 1 H) , 8.05 (s, 1H) , 8.18 (d, J = 7.4 *Hz*, 1 H) .

Ejemplo 135

Trifluoroacetato de 3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - (metiloxi) fenil]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó 2 - [2 - (metiloxi) fenil]etanamina en el desplazamiento y HPLC con TFA (rendimiento: 33%) . LC - MS m/z 628 $(M+H)^+$; ^1H - NMR (MeOD) 2.38 (s, 3 H) , 2.70 (s, br, 2 H) , 3.30 (m, 2 H) , 3.77 (s, 3 H) , 4.16 (m, 2 H) , 6.89 (m, 3H) , 7.18 (m, 4 H) , 7.57 (m, 3 H) , 7.98 (s, 1H) , 8.12 (d, J = 8.0 *Hz*, 1 H) .

Ejemplo 136

3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (propilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 118c excepto que se utilizó amina de propilo en el desplazamiento y HPLC con TFA (rendimiento: 29%) . LC - MS m/z 536 $(M + H)^+$; ^1H - NMR (MeOD) 0.77 (s, 3 H) , 1.45 (m, 2H) , 2.44 (s, 3 H) , 3.09 (s, 2 H) , 4.23 (m, 2 H) , 7.23 (m, 3 H) , 7.60 (m, 2H) , 7.68 (m, 1 H) , 8.08 (s, 1 H) , 8.20 (d, $J = 8.0$ *Hz*, 1 H) .

Ejemplo 137

3 - [8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - fenilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó anilina en la reacción de acople de amidas (rendimiento: 45%) . LC - MS m/z 558 $(M + H)^+$; ^1H - NMR (MeOD) 2.36 (s, 3 H) , 2.77 (s, 6H) , 3.15 (s, 2 H) , 3.55 (m, 2 H) , 4.20 (m, 2 H) , 7.18 (m, 3 H) , 7.38 (m, 2H) , 7.56 (m, 2 H) , 7.71 (m, 2H) , 7.84 (s, 1 H) , 8.01 (d, $J = 8.0$ *Hz*, 1 H) .

Ejemplo 138

N - (3,4 - difluorofenil) - 3 - [8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó anilina de 3,4 - difuoro la reacción de acople de amidas (rendimiento: 15%) . LC - MS m/z 594 $(M + H)^+$; ^1H - NMR (MeOD) 2.36 (s, 3 H) , 2.77 (s, 6H) , 3.16 (s, 2 H) , 3.55 (m, 2 H) , 4.19 (m, 2 H) , 7.24 (m, 3 H) , 7.50 (m, 3 H) , 7.86 (m, 2 H) , 8.00 (m, 1H) .

Ejemplo 139

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - 3 - piridinilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó 3 - piridinamina en la reacción de acople de amidas (rendimiento: 6%) . LC - MS m/z 559 $(M + H)^+$; ^1H - NMR (MeOD) 2.14 (s, 6 H) , 2.35 (m, 5H) , 3.24 (m, 2 H) , 4.14 (m, 2 H) , 7.15 (m, 2 H) , 7.50 (m, 3 H) , 7.87 (s, 1 H) , 8.01 (m, 1 H) , 8.30 (m, 2H) , 8.92 (s, 1H) .

Ejemplo 140

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - *N* - [6 - (metiloxi) - 3 - piridinil]benzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó 6 - (metiloxi) 3 - piridinamina en la reacción de acople de amidas (rendimiento: 65%) . LC - MS m/z 589 $(M + H)^+$; ^1H - NMR (MeOD) 2.12 (s, 6 H) , 2.33 (m, 5 H) , 3.21 (m, 2 H) , 3.92 (s, 3 H) , 4.11 (m, 2 H) , 6.38 (d, J = 8.8 *Hz*, 1 H) , 7.14 (m, 2 H) , 7.50 (d, J = 8.0 *Hz*, 2 H) , 7.82 (s, 1H) , 7.98 (m, 2H) , 8.44 (s, 1H) .

Ejemplo 141

Ácido 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etilbenzóico

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 117 excepto que se utilizó ácido 3 - (dihidroxiboranil) - 4 - etilbenzóicoen la reacción de acople

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(rendimiento: 38%) . LC - MS m/z 497 $(M + H)^+$; ^1H - NMR (MeOD) 1.22 (t, $J = 7.6$ *Hz*, 3 H) , 2.68 (s, 2 H) , 2.77 (s, 6 H) , 3.16 (m, 2 H) , 3.53 (m, 2 H) , 4.13 (m, 2 H) , 7.18 (m, 2H) , 7.55 (m, 2 H) , 7.86 (s, 1H) , 8.10 (m, 1H) .

Ejemplo 142

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etil - *N* - (4 - fluorofenil) benzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 125 excepto que se utilizó ácido 3 - (8 - (2 - ,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etilbenzóico como el ácido y se utilizo 4 - fluoroanilina s e utilizo como la amina para la reacción de acople de amidas y HPLC como TFA (rendimiento: 56%) . LC - MS m/z 590 $(M + H)^+$; ^1H - NMR (MeOD) 1.22 (t, $J = 7.6$ *Hz*, 3 H) , 2.69 (s, 2 H) , 2.77 (s, 6 H) , 3.15 (m, 2 H) , 3.54 (m, 2 H) , 4.13 (m, 2 H) , 7.15 (m, 4H) , 7.53 (m, 1 H) , 7.60 (d, $J = 8.0$ *Hz*, 1H) , 7.72 (m, 2H) , 7.80 (s, 1H) , 8.05 (m, 1H) .

Ejemplo 143

N - 3,4 - difluorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etillbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 142 excepto que se utilizó 3,4 - difluoroanilina en la reacción de acople de amidas y HPLC con THF (rendimiento: 54%) . LC - MS m/z 608 $(M + H)^+$; ^1H - NMR (MeOD) 1.24 (t, $J = 7.6$ *Hz*, 3 H) , 2.69 (s, 2 H) , 2.77 (s, 6 H) , 3.15 (m, 2 H) , 3.54 (m, 2 H) , 4.18 (m, 2 H) , 7.24 (m, 3H) , 7.54 (m, 3 H) , 7.85 (m, 2H) , 8.05 (m, 1H) .

Ejemplo 144

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etill - N - 1,3 - tiazol - 2 - ilbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 142 excepto que se utilizó 1,3 - tiazol - 2 - amina en la reacción de acople de amidas y HPLC con THF (rendimiento: 43%). LC - MS m/z 579 $(M + H)^+$; ^1H - NMR (MeOD) 1.25 (t, $J = 7.6$ *Hz*, 3 H), 2.71 (s, 2 H), 2.77 (s, 6 H), 3.16 (m, 2 H), 3.56 (m, 2 H), 4.18 (m, 2 H), 7.20 (m, 3H), 7.55 (m, 2 H), 7.66 (m, 1 H), 7.90 (s, 1H), 8.14 (m, 1H).

Ejemplo 145

Trifluoroacetato de N - 1,3 - benzodiozol - 5 - il - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparo mediante el Procedimiento General para acoplamientos HATU. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1% TFA) proporcionó el compuesto del titulo 4.9 mg (23%). LC - MS m/z 602 $(M + H)^+$

Ejemplo 146

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - etillbenzamida

El compuesto del titulo se preparó mediante el procedimiento en el ejemplo 142 excepto que se utilizó amoniaco en la reacción de acople de amidas y HPLC sin THF (rendimiento: 64%). LC - MS m/z 496 $(M + H)^+$; ^1H - NMR (MeOD) 1.23 (m, 3 H), 2.13 (s, 6 H), 2.35 (m, 2 H), 2.66 (m, 2 H), 3.26 (m, 2 H), 4.12 (m, 2 H), 7.15 (m, 2 H), 7.51 (m, 2 H), 7.73 (s, 1 H), 7.94 (m, 1H).

Ejemplo 147

{1 - [8 - (2,6 - difluorofenil) - 4 - (2 - metil - 5 - {[(fenilmetil) amino]carbonil}fenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - piperidinil}metilcarbamato de 1,1 - dimetiletilo

El compuesto 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - (fenilmetil) benzamida (0.0811 g, 0.144 mmol) se disolvió en CH_2Cl_2 (5 mL) y metil (4 - piperidinil) carbamato de 1,1 - dimetiletil (0.0394 g, 0.18 mmol) y se agregó trietilamina (0.029 g, 0.288 mmol) . La mezcla de reacción se agitó durante 4 días. Se agregó metil - (4 - piperidinil) carbamato de 1,1, - dimetiletil (0.0788 g, 0.36 mmol) y trietilamina (0.058 g, 0.576 mmol) adicionales y la mezcla se agitó bajo argón a temperatura ambiente durante 7 días adicionales. Los solventes se bombearon al vacío, y el residuo se absorvió en EtOAc y se lavó con NaOH 1N, salmuera, se secó sobre Na2SO4 anhidro se filtró y evaporó. El residuo se cromatografió sobre gel de sílice (20 g) se eluyo con 0 - 70% EtOAc / hexano para proporcionar el compuesto del titulo. Permanecieron algunas impuridades, de manera que el material se cromatografió nuevamente sobre gel de sílice (20 g) eluido con 0 - 50 % EtOAc / hexano para proporcionar el compuesto del titulo como un sñolido amorfíco blanco. mp (dec 146 - 150 °C. LC - MS m/z 698 $(M+H)^+$, 2.66 minutos (tiempo de ret) .

Ejemplo 148

3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metil - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - 4 - metil - N - (fenilmetil) benzamida

El 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - 4 - metil - *N* - (fenilmetil) benzamida (0.056 g, 0.1 mmol) se disolvió en THF (5 mL) y se agregó 1 - metilpiperazina (0.0303 g, 0.3 mmol) . Los solventes se bombearon al vacío y el residuo se

absorvió en EtOAc y se lavó con NaOH 1 N, salmuera, se seco sobre Na_2SO_4 anhidro se filtró y evaporó. El residuo se cromatografió sobre gel de sílice (20 g) eluyendo con 6 : 0.1 : 0.01 a 6 : 0.3 : 0.03, CH_2Cl_2 : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 164 - 168°C. LC - MS m/z 584 $(M+H)^+$ 1.85 minutos (tiempo de ret).

Ejemplo 149

3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metil) - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N,N*,4 - trimetilbenzamida

149a) 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - N,N,4 - trimetilbenzamida

Se absorvió ácido 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzóico (1 g, 3.8 mmoles) en CH_2Cl_2 (200 mL) y se trató con cloruro de oxalilo (0.44 mL, 5 mmol) y DMF (1 gota). Una hora luego que evolución de gas hubiera cesado, los solventes se bombearon al vacío, y el residuo se separo del tolueno. Esto se quitó de nuevo en CH_2Cl_2 (200 mL), y amina de dimetil en exceso se burbujeó en la mezcla, la cual se selló y agitó durante la noche a temperatura ambiente. Los solventes se bombearon para proporcionar la *N,N*,4 - trimetil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida cruda, el cual se utilizó en el proximo paso sin purificación adicional.

5 - cloro - (2,6 - difluorofenil) - 7 - (metiltio) - 3,4 - dihidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 2 (1H) - ona (0.102 g, 0.298 mmol), *N,N*,4 - trimetil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida del anterior, (0.129 g, 0.447 mmol), K_2CO_3 (0.123 g, 0.894 mmol), se quitaron en dioxano (6 mL) y agua 1.2 mL). La mezcla se desgasificó con argón durante 30 minutos y se agregó tetrakis (trifenil - fosfina) paladio (0) (0.026 g, 0.022 mmol). Luego la mezcla se agitó bajo argón a 95 °C durante 18 horas. Los solventes se bombearon, y luego de concentración acuosa el material crudo se cromatografió en gel de sílice (15 g), eluyendo con un gradiente EtOAc / CH_2Cl_2 para proporcionar el compuesto del titulo como un sólido amorfico blanco. mp 144 - 147°C. LC - MS m/z 470 $(M+H)^+$ 2.02 minutos (tiempo ret).

149b) 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il]ulfonil) - *N,N*,4 - trimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 2 - il] - 4 - pirimidin - 4 - il]ulfonil) - N,N,4 - trimetilbenzamida (0.089 g, 0.19 mmol) se disolvió wn CH_2Cl_2 (10 mL) y se agregó 50 - 60% ácido 3 - cloroperoxibenzóico (0.118 g, 0.38 mmol) y la mezcla se agitó durante la noche. Los solventes se bombearon, y el residuo se cromatografió sobre gel de sílice eluyendo con CH_2Cl_2 - 90% EtOAc / CH_2Cl_2 para proporcionar 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il]ulfonil) - *N,N*,4 - trimetilbenzamida. LC - MS m/z 502 $(M+H)^+$, 1.78 minutos (tiempo de ret).

149c) 3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metil - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N,N*,4 - trimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il]ulfonil) - *N,N*,4 - trimetilbenzamida (0.050 g, 0.1 mmol) se disolvió en THF (5 mL) y se agregó 1 - metilpiperazina (0.050 g, 0.5 mmol). La reacción se agitó bajo argón durante la noche. Los solventes se bombearon al vacío. El residuo se cromatografió en gel de sílice (15 g) eluido con CH_2CL_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 159 - 162°C. LC - MS m/z 522 $(M+H)^+$ 1.59 minutos (tiempo de ret).

Ejemplo 150

Trifluoroacetato de N - 4 - bifenilil - 3 - [8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il) - 4 - metilbenzamida

Se preparo mediante el Procedimiento General para Acoplamientos HATU. La HPLC de fase inversa (10 - 9% gradiente de acetanitrilo en agua con 0.1% TFA) proporcionó el compuesto del titulo 4.4 mg (19%). LC - MS m/z 634 $(M+H)^+$.

Ejemplo 151

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (dimetilamino) propil]amino - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il) - 4 - metil - *N* - (fenilmetil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - 4 - metil - *N* - (fenilmetil) benzamida (0.056 g, 0.1 mmol) se disolvió en THF (5 mL) y se agregó N,N - dimetil - 1,3 - propanediamina (0.035 g, 0.3 mmol) . La reacción se llevó a cabo y se concentró como en el Ejemplo 148 para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 141 - 144 °C. LC - MS m/z 586 $(M+H)^+$ 1.52 minutos (tiempo de ret) .

Ejemplo 152

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,*N*,4 - trimetilbenzamida

La reacción se llevó a cabo y se concentró como en el Ejemplo 149c excepto que se sustituyó etilaminino de dimetilamino (0.044 g, 0.5 mmol) por 1 - metilpiperazina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 138 - 142 °C. LC - MS m/z 510 $(M+H)^+$ 1.31 minutos (tiempo de ret) .

Ejemplo 153

3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - [(1 - metilrtil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N*,*N*,4trimetilbenzamida

La reacción se llevo a cabo y se concentró como en el Ejemplo 149c excepto que se sustituyo (2 - aminoetil) (1 - metiletil) amina (0.051 g, 0.5 mmol) por 1 - metilpiperazina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 130 - 133 °C. LC - MS m/z 524 $(M+H)^+$ 1.36 minutos (tiempo de ret) .

Ejemplo 154

3 - (8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il} - *N*,*N*,4 - trimetilbenzamida

La reacción se llevo a cabo y se concentró como en el Ejemplo 149c excepto que se sustituyo [3 - (dimetilamino) propil]metilamina (0.058 g, 0.5 mmol) por 1 - metilpiperazina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 114 - 118 °C. LC - MS m/z 538 $(M+H)^+$ 1.49 minutos (tiempo de ret) .

Ejemplo 155

3 - {8 - (2,6 - difluorofenil) - 2 - [(1 - metil - 4 - piperinidil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il} - *N*,*N*,4 - trimetilbenzamida

La reacción se llevo a cabo y se concentró como en el Ejemplo 149c excepto que se sustituyo 1 - metil - 4 - piperidinamina (0.057 g, 0.5 mmol) por 1 - metilpiperazina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 163 - 165 °C. LC - MS m/z 536 $(M+H)^+$ 1.25 minutos (tiempo de ret).

Ejemplo 156

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il) - *N*,*N* - dietil - 4 - metilbenzamida

156a) 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N*,*N* - dietil - 4 - metilbenzamida

La reacción se llevo a cabo y se concentró como en el Ejemplo 149c excepto que se adiciono dietilamina de exceso en vez de dietilaminapara proporcionar el *N*,*N* - dietil - 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida cruda. Esto se cromatografió en gel de sílice (100 g) eluido con un gradiente de acetato de etilo de cloruro para proporcionar *N*,*N* - dietil - 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida limpio. LC - MS m/z 470 $(M+H)^+$ 2.40 minutos (tiempo de ret).

5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metiltio) - 3 - ,4 - dihidropirimido[4,5 - *d*]pirimidin - 2 - (1H) - ona (0.720 g, 2.1 mmol), *N*,*N* - dietil - 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzamida del anterior (1.09 g, 3.15 mmol) y K_2CO_3 (0.868 g, 6.3 mmol), se absorbieron en dioxano (42 mL) y agua (8.5 mL). La mezcla se degasificó en argón durante 30 minutos y se agregó tetrakis - (trifenilfosfino) paladio (0) (0.183 g, 0.15 mmol). Luego la mezcla se calentó bajo argón a 95 °C durante 18 horas. Los solventes se bombearon y luego de la concentración acuosa, el material cruda se cromatografió en gel de sílice (150 g) eluido con un gradiente EtOAc / CH_2Cl_2 para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 127 - 129 °C. LC - MS m/z 498 $(M+H)^+$ 2.11minutos (tiempo de ret).

159b) 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N,N* - dietil - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimin[4,5 - *d*]pirimidin - 2 - il] - 4 - pirimidin - 4 - il] - *N,N* - dietil - 4 - metilbenzamida (0.63g, 1.26 mmol) se disolvió en CH2CL2 (100Ml) y se agregó 50 - 60% ácido 3 - cloroperoxibenzóico (0.786g, 2.52 mmol) y la mezcla se agitó durante la noche. Los solventes se bombearon,y el residuo se cromatografió en gel de sílice eluido con CH2Cl2 - 90% EtOAc/CH2Cl2 para proporcionar el compuesto del titulo con un sólido amorfo blanco. mp 132 - 135°C. LC - MS m/z 530 $(M+H)^+$,1.81 minutos (tiempo de ret).

156c) 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N,N* - dietil - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N,N* - dietil - 4 - metilbenzamida (0.053g, 0.1 mmol) se disolvio en THF (5 mL) y se agregó dimetilaminoetilamina. (0.044 g, 0.5 mmol). La reacción se agito bajo argón durante la noche. Los solventes se bombearon al vacio, y el residuo se cromatografió sobre gel de sílice (15 g) eluido con CH2Cl2 para 6:0.5:0.05, CH_2Cl_2: etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. Mp 125 - 127°C. LC - MS m/z 538 $(M+H)^+$ (tiempo de ret).

Ejemplo 157

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - [4 - (etiloxi) fenil] - 4 - metilbenzamida

Se preparó mediante el Procedimiento General para acoplamientos HATU. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 5.1 mg (24 %). LC - MS m/z 602 $(M+H)^+$.

Ejemplo 158

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - N - [4 - (metiloxi) fenil]benzamida

Se preparó mediante el Procedimiento General para acoplamientos HATU. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 3.4 mg (16 %). LC - MS m/z 588 $(M+H)^+$.

Ejemplo 159

3 - {8 - (2,6 - difluorofenil) - 2 - [(1 - metil - 4 - piperidinil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - *N,N* - dietil - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N,N* - dietil - 4 - metilbenzamida (0.053 g, 0.1 mmol) se disolvio en THF (5 mL) y se agregó 1 - metil - 4 - piperidinamina (0.044 g, 0.5 mmol). La reacción se agitó bajo argón durante la noche. Los solventes se bombearon al vacío, y el residuo se purificó mediante cromatografía auto preparativa dirigida por masa. Las fraccines se evaporaron, y la concentración básica acuosa proporcionó el compuesto del titulo como un sólido amorfo blanco. mp 165 - 169°C. LC - MS m/z 564 $(M+H)^+$, 1.44 minutos (tiempo de ret).

Ejemplo 160

3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - [(1 - metiletil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,N - dietil - 4 - metilbenzamida

La reacción se llevó a cabo y se concentró como en el ejemplo 156c excepto que se sustituyo (2 - aminoetil) (1 - metiletil) amina (0.051 g, 0.5 mmol) por dimetilaminoetilamina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 89 - 91°C. LC - MS m/z 552 $(M+H)^+$, 1.32 minutos (tiempo de ret).

Ejemplo 161

3 - {8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - *N,N* - dietil - 4 - metilbenzamida

La reacción se llevó a cabo y se concentró como en el ejemplo 156c excepto que se sustituyo [3 - (dimetilamino) propil]metilamina (0.058 g, 0.5 mmol) por dimetilaminoetil - amina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp 106 - 108°C. LC - MS m/z 566 $(M+H)^+$, 1.69 minutos (tiempo de ret).

Ejemplo 162

3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metil - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - N,N - dietil - 4 - metilbenzamida

La reacción se llevó a cabo y se concentró como en el ejemplo 156c excepto que se sustituyo 1 - metilpiperazina (0.05 g, 0.5 mmol) por dimetilaminoetilamina para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec 201 - 205°C. LC - MS m/z 550 $(M+H)^+$, 1.35 minutos (tiempo de ret) .

Ejemplo 163

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,4 - dimetilbenzamida

163a) 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

Ácido 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilbenzóico (0.59 g, 1.33 mmol) se absorvió en CH_2Cl_2 (75 mL) , se agregó diisopropilletilamina (0.7 mL, 4 mmol) seguido por HATU (0.556 g, 1.46 mmol) . Metilamina gaseosa se burbujeó lentamente hasta que se completo la reacción. Concentración acuosa seguida por cromatografía en gel de sílice (100 g) eluida con CH_2Cl_2 – 90% EtOAc/CH_2Cl_2 proporcionó el compuesto del titulo como un sólido amorfo blanco. mp 273 - 275°C. LC - MS m/z 456 $(M+H)^+$, 1.85 minutos (tiempo de ret.) .

163b) 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida, (0.592 g, 1.3 mmol) se absorvió en CH_2Cl_2 (75 mL) , y se agregó 50 - 63% ácido 3 - cloroperoxibenzóico (0.84 g, 2.7 mmol) . La mezcla se agitó durante la noche bajo argón. El solvente se bombeó al vacío, y el residuo se cromatograficó sobre sílice (80 g) eluido con 0 - 10% MeOH/CH_2Cl_2. La criztalización a partir de MeOH proporcionó el compuesto del titulo como un sólido cristalino. Mp 275 - 278°C. LC - Ms m/z 488 $(M+H)^+$, 1.58 minutos (tiempo de ret.) .

163c) 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,4 - dimetilaminobenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.03 g, 0.06 mmol) se disolvió en THF (5 mL) y se agregó dimetilaminoetilamina (0.026 g, 0.3 mmol). La reacción se agitó bajo argón durante la noche. Los solventes se bombearon al vacío, y el residuo se cromatografió sobre gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido blanco amorfo. Mp (dec) 155 - 158C. LC - MS m/z 496 $(M+H)^+$, 1.29 minutos (tiempo de ret.).

Ejemplo 164

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (diemtilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (3 - metilfenil) benzamida

Se preparó mediante el Procedimiento General para acoplamientos HATU. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1% TFA) proporcionó el compuesto 4.5 mg (21 %). LC - MS m/z 583 $(M + H)^+$.

Ejemplo 165

N - (2,4 - difluorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó mediante el Procedimiento General para acoplamientos HATU. Extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución y finalmente metanol proporcionó el compuesto 5 mg (23 %). LC - MS m/z 594 $(M+H)^+$.

Ejemplo 166

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (dimetilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - N,4 - dimetilbenzamida (0.032 g, 0.031 mmol) se disolvió en THF (5 mL) y se agregó *N,N* - dimetil - 1,3 - propanediamina (0.032 g, 0.31 mmol) . La reacción se agitó bajo argón durante la noche. Los solventes se bombearon al vacío, y el residuo se cromatografió sobre gel de sílice (15 g) eluyendo con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 164 - 167°C. LC - MS m/z 510 $(M+H)^+$, 1.31 minutos (tiempo de ret.)

Ejemplo 167

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1 - metiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.031 g, 0.064 mmol) se disolvió en THF (5 mL) y se agregó (2 - aminoetil) (1 - metiletil) amina (0.032 g, 0.31 mmol) . La reacción se agitó bajo argón durante 10 dias. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 136 - 139°C. LC - MS m/z 510 $(M+H)^+$, 1.35 minutos (tiempo de ret.) .

Ejemplo 168

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1 - metiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.036 g, 0.074 mmol) se disolvió en THF (5 mL) y se agregó (3 - aminopropil) (1 - metiletil) amina (0.045 g, 0.37 mmol) . La reacción se agitó bajo argón durante la noche. Los solventes se bombearon al vacío, y el residuo se cromatografió sobre gel de sílice (15 g) eluyendo con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 153 - 157°C. LC - MS m/z 524.6 $(M+H)^+$, 1.31 minutos (tiempo de ret.) .

Ejemplo 169

3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metil - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.033 g, 0.0678 mmol) se disolvió en THF (5 mL) y se agregó 1 - metilpiperazina (0.034 g, 0.34 mmol) . La reacción se calentó a 45 °C durante 4 horas y luego se enfrió a temperatura ambiente durante la noche. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 164 - 168°C. LC - MS m/z 508 $(M+H)^+$, 1.34 minutos (tiempo de ret.) .

Ejemplo 170

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1,1 - dimetiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.036 g, 0.074 mmol) se disolvió en THF (5 mL) y se agregó (3 - aminopropil) (1,1 - dimetiletil) amina (0.045 g, 0.37 mmol) . La reacción se calentó bajo argón durante 2 días. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 166 - 170°C. LC - MS m/z 538 $(M+H)^+$, 1.38 minutos (tiempo de ret.) .

Ejemplo 171

3 - [2 - {[3 - (dibutilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.03 g, 0.062 mmol) se disolvió en THF (5 mL) y se agregó (3 - aminopropil) dibutilamina (0.058 g, 0.31 mmol) .

La reacción se agitó bajo argón durante 24 horas. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 112 - 115°C. LC - MS m/z 594.6 $(M+H)^+$, 1.59 minutos (tiempo de ret.).

Ejemplo 172

3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.03 g, 0.062 mmol) se disolvió en THF (5 mL) y se agregó (3 - aminopropil) dietilamina (0.041 g, 0.31 mmol). La reacción se agitó bajo argón durante 24 horas. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (15 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 133 - 136°C. LC - MS m/z 538 $(M+H)^+$, 1.34 minutos (tiempo de ret.).

Ejemplo 173

3 - {8 - (2,6 - difluorofenil) - 2 - [(1 - metil - 4 - piperidinil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.02 g, 0.041 mmol) se disolvió en THF (5 mL) y se agregó 1 - metil - 4 - piperidinamina (0.024 g, 0.21 mmol). La reacción se agitó a temperatura ambiente durante 24 horas, pero la reacción no se completo. La reacción se calentó a 45 °C durante 24 horas y luego se enfrió a temperatura ambiente. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (10 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 205 - 209°C. LC - MS m/z 522 $(M+H)^+$, 1.29 minutos (tiempo de ret.).

Ejemplo 174

3 - {8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.02 g, 0.041 mmol) se disolvió en THF (5 mL) y se agregó [3 - (dimetiletil) propil]metilamina (0.024 g, 0.205 mmol) . La reacción se agitó a temperatura ambiente durante 6 días, pero la reacción no se completo. La reacción se calentó a 45°C durante la noche y luego se enfrió a temperatura ambiente. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (10 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 163 - 165°C. LC - MS m/z 524.6 $(M+H)^+$, 1.47 minutos (tiempo de ret.) .

Ejemplo 175

3 - {8 - (2,6 - difluorofenil) - 7 - oxo - 2 - [4 - (1 - pirrolidinil) - 1 - piperidinil] - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.015 g, 0.031 mmol) se disolvió en THF (5 mL) y se agregó 4 - (1 - pirrolidinil) piperidina (0.024 g, 0.155 mmol) . La reacción se agitó a temperatura ambiente durante 4 días. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (10 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol : NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 189 - 194°C. LC - MS m/z 562 $(M+H)^+$, 1.62 minutos (tiempo de ret.) .

Ejemplo 176

3 - [2 - (1,4' - bipiperidin - 1' - il) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - *N*,4 - dimetilbenzamida (0.015 g, 0.031 mmol) se disolvió en THF (5 mL) y se agregó 1,4' - bipiperidina (0.026 g, 0.115 mmol) . La reacción se agitó a temperatura ambiente durante 4 días. Los solventes se bombearon al vacío, y el residuo se cromatografió en gel de sílice (10 g) eluido con CH_2Cl_2 a 6 : 0.5 : 0.05, CH_2Cl_2 : etanol :

NH_4OH para proporcionar el compuesto del titulo como un sólido amorfo blanco. mp (dec) 179 - 184°C. LC - MS m/z 576 $(M+H)^+$, 1.54 minutos (tiempo de ret.).

Ejemplo 177

Trifluoroacetato de 3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [metil (fenil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 5 mg (19%). LC - MS m/z 600 $(M+H)^+$.

Ejemplo 178

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (metiloxi) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 6.2 mg (28%). LC - MS m/z 511 $(M+H)^+$.

Ejemplo 179

Trifluoroacetato de 3 - [8 - (2,6 - difluorofenil) - 2 - (4 - metilhexahidro - 1H - 1,4 - diazepin - 1 - il) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 8.55 mg (35%). LC - MS m/z 550 $(M+H)^+$.

Ejemplo 180

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - (4 - etil - 1 - piperazinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 8.5 mg (35%). LC - MS m/z 550 $(M+H)^+$.

Ejemplo 181

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - (2 - fluorofenil) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguida por acetato de etilo, 20 % metanol/acetato de etilo proporcionó el compuesto del titulo 4.6 mg (22%). LC - MS m/z 576 $(M+H)^+$.

Ejemplo 182

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[hexadrino - 1H - azepin - 1 - il) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 12 mg (46%). LC - MS m/z 592 $(M+H)^+$.

Ejemplo 183

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[3 - (1 - pirrolidinil) propil]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 11 mg (44%). LC - MS m/z 564 $(M+H)^+$.

Ejemplo 184

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[(3S) - 1 - (fenilmetil) - 3 - pirrolidin]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 11.4 mg (42%). LC - MS m/z 612 $(M+H)^+$.

Ejemplo 185

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - ({[(2S) - 1 - etil - 2 - pirrolidinil]metil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 9.1 mg (37%). LC - MS m/z 564 $(M+H)^+$.

Ejemplo 186

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) - 1 - metiletil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 11.1 mg (47%). LC - MS m/z 538 $(M+H)^+$.

Ejemplo 187

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (1 - metil - 2 - pirrilidinil) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 12.2 mg (49%). LC - MS m/z 564 $(M+H)^+$.

Ejemplo 188

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[2 - (1 - piperidinil) etil]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 13.8 mg (56%) . LC - MS m/z 564 $(M+H)^+$.

Ejemplo 189

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (1H - imidazol - 1 - il) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 12.3 mg (50%) . LC - MS m/z 561 $(M+H)^+$.

Ejemplo 190

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - hidroxi - 1 - (hidroximetil) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 3.4 mg (15%) . LC - MS m/z 527 $(M+H)^+$.

Ejemplo 191

Trifluoroacetato de 3 - [2 - ({2 - [bis (1 - metiletil) amino]etil}amino) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 6.5 mg (25%) . LC - MS m/z 580 $(M+H)^+$.

Ejemplo 192

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 4.1 mg (20%) . LC - MS m/z 579 $(M+H)^+$.

Ejemplo 193

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - 4 - piridinilenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 2.6 mg (13%) . LC - MS m/z 559 $(M+H)^+$.

Ejemplo 194

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[2 - (penilamino) etil]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 14 mg (56%) . LC - MS m/z 572 $(M+H)^+$.

Ejemplo 195

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[1 - fenil - 2 - (1 - pirrolidinil) etil]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 9.2 mg (33%) . LC - MS m/z 626 $(M+H)^+$.

Ejemplo 196

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[2 - fenil - 2 - (1 - pirronidinil) etil}amino}5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 9.2 mg (33%) . LC - MS m/z 626 $(M+H)^+$.

Ejemplo 196

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7oxo - 2 - {[2 - fenil - 2 - (1 - pirrolidinil) etil]amino} - ,5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 6.1 mg (22%) . LC - MS m/z 626 $(M+H)^+$.

Ejemplo 197

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - ({2 - [4 - (fenilmetil) - 1 - piperazinil]etil}amino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 12.5 mg (43%) . LC - MS m/z 655 $(M+H)^+$.

Ejemplo 198

Trifluoroacetato de 3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (4 - propil - 1 - piperazinil) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 3.4 mg (14%) . LC - MS m/z 564 $(M+H)^+$.

Ejemplo 199

Trifluoroacetato de 3 - [2 - (4 - butil - 1 - piperazinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 9 mg (35%) . LC - MS m/z 578 $(M+H)^+$.

Ejemplo 200

3 - (8 - (2,6 - difluorofenil) - 7 - oxo - 2 - {[1 - (fenilmetil) - 4 - piperidinil]amino} - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa sin TFA proporcionó el compuesto del titulo 6.7 mg (24%) . LC - MS m/z 626 $(M+H)^+$.

Ejemplo 201

3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (2 - propen - 1 - ilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa sin TFA proporcionó el compuesto del titulo 3 mg (14%) . LC - MS m/z 493 $(M+H)^+$.

Ejemplo 202

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - 3 - isoquinilinil - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 4.7 mg (21%) . LC - MS m/z 609 $(M+H)^+$.

Ejemplo 203

Trifluoroacetato de 3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - [etil (3 - metilfenil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 9.8 mg (36%) . LC - MS m/z 614 $(M+H)^+$.

Ejemplo 204

Trifluoroacetato de 3 - [2 - [[2 - (dietilaminoetil] (metil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

Se preparó siguiendo el Procedimiento General para desplazamiento de sulfoxidos. La HPLC de fase inversa (10 - 90% gradiente de acetonitrilo en agua con 0.1 % TFA) proporcionó el compuesto del titulo 5.5 mg (22%) . LC - MS m/z 566 $(M+H)^+$.

Ejemplo 205

N - (4 - cianofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 2.4 mg (11%) . LC - MS m/z 583 $(M+H)^+$.

Ejemplo 206

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [3 - (metiltio) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 3.6 mg (17%) . LC - MS m/z 604 $(M+H)^+$.

Ejemplo 207

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [4 - (fenilcarbonil) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 3.2 mg (13%). LC - MS m/z 662 $(M+H)^+$.

Ejemplo 208

4 - ({[3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilfenil]carbonil}amino) benzoato de butilo

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 4 mg (17%). LC - MS m/z 658 $(M+H)^+$.

Ejemplo 209

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [4 - (1 - piperidinilsulfonil) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 2.3 mg (9%). LC - MS m/z 704 $(M+H)^+$.

Ejemplo 210

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [4 - (feniloxi) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 3.2 mg (14%). LC - MS m/z 650 $(M+H)^+$.

Ejemplo 211

N - [3 - (aminocarbono) fenil] - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.5 mg (25%). LC - MS m/z 601 $(M+H)^+$.

Ejemplo 212

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - (2,3 - dihidro - 1,4 - benzodixin - 6 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 8 mg (36%). LC - MS m/z 616 $(M+H)^+$.

Ejemplo 213

Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (2 - metifenil) benzamid

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 7.1 mg (35%) . LC - MS m/z 571 $(M+H)^+$.

Ejemplo 214

N - (3 - cianofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.4 mg (26%) . LC - MS m/z 583 $(M+H)^+$.

Ejemplo 215

N - (3,5 - difluorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 3.6 mg (17%) . LC - MS m/z 594 $(M+H)^+$.

Ejemplo 216

N - (3 - clorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5 mg (23%) . LC - MS m/z 592 $(M+H)^+$.

Ejemplo 217

N - (3 - cloro - 4 - fluorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 6.8 mg (31%) . LC - MS m/z 610 $(M+H)^+$.

Ejemplo 218

N - (4 - clorofenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 6.8 mg (32%) . LC - MS m/z 592 $(M+H)^+$.

Ejemplo 219

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - [4 - (dimetilamino) fenil] - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 9 mg (42%) . LC - MS m/z 601 $(M+H)^+$.

Ejemplo 220

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [4 - (trifluorometil) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato

de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.8 mg (26%) . LC - MS m/z 626 $(M+H)^+$.

Ejemplo 221

N - (4 - acetilfenil) - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 4.4 mg (20%) . LC - MS m/z 600 $(M+H)^+$.

Ejemplo 222

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - [3 - (feniloxi) fenil]benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.7 mg (24%) . LC - MS m/z 650 $(M+H)^+$.

Ejemplo 223

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - 1H - indazol - 6 - il - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 9.3 mg (43%) . LC - MS m/z 598 $(M+H)^+$.

Ejemplo 224

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metil - N - (2 - metil - 1,3 - benzotiazol - 5 - il) benzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.3 mg (23%) . LC - MS m/z 629 $(M+H)^+$.

Ejemplo 225

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - N - (4' - fluor - 3 - bifenilil) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 4 mg (17%) . LC - MS m/z 652 $(M+H)^+$.

Ejemplo 226

N - [3 - (aminosulfonil) fenil] - 3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il) - 4 - metilbenzamida

Se preparó siguiendo el Procedimiento General para acoplamientos HATU. La extracción de fase sólida (SPE, aminopropil, 500 mg) mediante elución con cloroformo seguido por acetato de etilo, 20% metanol/acetato de etilo y finalmente metanol proporcionó el compuesto del titulo 5.5 mg (24%) . LC - MS m/z 637 $(M+H)^+$.

Ejemplo 227

3 - [2 - [(3 - aminopropil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida

227a) 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida

A una suspensión agitada de Oxona (817.96 g, 1.33 mol, 3 eq) en agua) 2142 mL, 10 vol) se agregó 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (214.21 g, 0.443 mol, 1 eq) suspendido en acetonitrilo (4284 mL) . La mezcla resultante se agitó a temperatura ambiente durante la noche. Luego la mezcla se filtró y el residuo se agitó secuencialmente con 5% metabisulfito de sodio (2 x 3000 mL) y agua (1 x 300 mL) . Luego el filtrado de la mezcla de reacción se diluyó con agua (2142 mL, 10 vol) . El sólido formado se recolectó mediante filtración. El sólido se lavó con agua y luego se secó en la bomba para proporcionar el compuesto del titulo. LC - MS m/z 516 $(M+H)^+$,2.77 minutos (timepo de ret.) . Se utilizó sin ninguna purificación adicional estando presente el sulfoxido correspondiente (aprox. 10%) .

227b) 3 - [2 - [(3 - aminopropil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida

A 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (497 mg, 1.0 mmol) en diclorometano (20 mL) se agregó 1,3 - propildiamina (0.251 mL,3.0 mL) . La mezcla se agitó durante la noche. La mezcla se concentró y se separó mediante cromatografía rápida para proporcionar el compuesto del titulo (395 mg, 78%) . LC - MS m/z 510 $(M+H)^+$.

227c) Trifluoroacetato de 3 - [2 - [(3 - aminopropil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida

A 3 - [2 - [(3 - aminopropil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (497 mg, 1.0 mmol) en diclorometano (20 mL) se agregó 1,3 - propildiamina (0.251 mL, 3.0 mL) . La mezcla se agitó durante la noche. La mezcla se concentró y separación inicial se llevó a cabo sin cromatografía rápida proporcionando el compuesto del titulo como una base libre (395 mg, 78%) . Luego la purificación adicional con una HPLC Glinson (con 0.1% TFA) proporcionó el compuesto del título (129.9 mg) . LC - MS m/z 510 $(M + H)^+$; ^1H - NMR (MeOD) δ 0.96 (t, $J = 7.40$ *Hz*, 3 H) , 1.56 – 1.66 (m, 3 H) , 1.72 (br, s, 2 H) , 2.31 (s, 3 H) , 2.77 (br, s, 2 H) , 3.22 (br, s, 2 H) , 3.33 (t, $J = 7.15$ *Hz*, 2 H) , 4.12 (br, s, 2 H) , 7.16 (t, $J = 8.41$ *Hz*, 2 H) , 7.44 – 7.59 (m, 2 H) , 7.73 (s, 1 H) , 7.87 (d,J = 8.03 Hz, 1 H) .

Ejemplo 228

Ácido 3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilbenzóico

228a) Trifluoroacetato de 5 - cloro - 7 - {[3 - (dietilamino) propil]amino} - 1 - (2,6 - difluorofenil) - 3,4 - dihidropirimido[4,5 - *d*]pirimidin - 2 (1*H*) - ona

A un 5 - cloro - 1 - (2,6 - difluorofenil) - 7 - (metilsulfonil) - 3,4 - dihidropirimido[4,5 - *d*]pirimidin - 2 (1*H*) - ona (275 mg, 0.767 mmol) en diclorometano (15 mL) se agregó N,N - dietil - 1,3 - propildiamina (0.181 mL, 1.15 mmol) y trietilamina (0.215 mL, 1.53 mmol) . La mezcla se agitó durante la noche. La mezcla se concentró y se separó mediante HPLC Wilson (con 0.1% TFA) para proporcionar el compuesto del titulo (207 mg, 64%) .

228b) Ácido 3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilbenzóico

A un 5 - cloro - 7 - {[3 - (dietilamino) propil]amino} - 1 - (2,6 - difluorofenil) - 3,4 - dihidropirimido[4,5 - *d*]pirimidin - 2 (1*H*) - ona (207 mg, 0.488 mmol) en 1,4 - dioxano (7.5 mL) y agua (2.5 mL) se agregó ácido 4 - metil - 3 - (4,4,5,5 - tetrametil - 1,3,2 - dioxaborolan - 2 - il) benzóico (0.192 g, 0.733 mmol) , tetrakis (trifenilfosfina) - paladio (0) (28.3 mg, 0.024 mmol) , y carbonato de potasio (270 mg) , 1.95 mmol) . La mezcla se calentó con microondas por 15 minutos a 150 °C, y luego se dejó enfriar a temperatura ambiente. La mezcla se concentró y separó mediante HPLC para proporcionar el compuesto del titulo (66 mg, 26%) . LC - MS m/z 525 $(M+H)^+$.

Ejemplo 229

N - (8 - (2,6 - difluorofenil) - 4 - {2 - metil - 5 - [(propilamino) carbonil]fenil} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 2 - il) - β - alanina

A 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 2 - il] - 4 - metil - *N* - propilbenzamida (100 mg, 0.2 mmol) en DMF (1 mL) se agregó β - alanina (35.6 mg, 0.4 mmol) y trietilamina (56.2 uL, 0.4 mmol) . La mezcla se calentó con un microondas a 100°C durante 2 horas. La mezcla se separó mediante HPLC para proporcionar el compuesto del titulo (45 mg, 43%) . LC - MS m/z 525 $(M+H)^+$.

Ejemplo 230

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamina) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il) - 4 - metil - N - propilbenzamida y la sal de trifluoroacetato correspondiente

230a) 3 - [2 - [(3 - cloropropil) amino] - 8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida

A 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (206 mg, 0.4 mmol) en DMF (4 mL) se agregó hidrocloruro de (3 - cloropropil) amina (78 mg, 0.6 mmol) y trietilamina (112 uL, 0.8 mmol) . La mezcla se calentó en un microondas a 60 °C durante 2 horas. La mezcla se separó mediante cromatografía rápida para proporcionar el compuesto del titulo (100 mg, 47%) .

230b) Trifluoroacetato de 3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il) - 4 - metil - *N* - propilbenzamida

A 3 - [2 - [(3 - cloropropil) amino] - 8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (100 mg, 0.189 mmol) en DMF (2 mL) se agregó etilamina (0.189 mL, 2.0 M en THF, 0.378 mmol) y carbonato de potasio (0.104 g, 0.756 mmol) . La mezcla se calentó con irradiaciones de microondas a 100°C durante aprox. 30 minutos. La mezcla se concentró y se separó mediante HPLC Wilson (con 0.1% TFA) proporcionando el compuesto del titulo (11 mg, 11%) . LC - MS m/z 538 $(M+H)^+$; ^1H - NMR (MeOD) δ 1.02 (t, *J* = 7.30 *Hz*, 3 H) , 1.08 (t, J = 6.92 *Hz*, 3 H) , 1.63 – 1.74 (m, 2 H) , 1.98 – 2.07 (m, 2 H) , 2.34 (s, 2 H) , 3.10 – 3.19 (m, 2 H) , 3.39 (t, J = 6.80 Hz, 4 H) , 3.43 – 3.52 (m, 1 H) , 3.53 – 3.64 (m, 1 H) , 3.78 (d, J = 15.86 *Hz*, 1 H) , 4.19 (d, J = 16.11 *Hz*, 1 H) , 7.13 (t, J = 8.31 Hz, 2 H) , 7.34 – 7.48 (m, 1 H) , 7.63 (d, J = 7.81 Hz, 1 H) , 7.79 (s, 1 H) , 7.99 (d, J = 8.06 Hz, 1 H) .

230c) 3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il) - 4 - metil - *N* - propilbenzamida

A 3 - [2 - [(3 - cloropropil) amino] - 8 - (2,6 - difluorofenil) - 2 - {[3 - (etilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*] pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida (265 mg, 0.50 mmol) en DMF (10 mL) se agregó etilamina (1.25 mL, 2.0 M en THF, 2.5 mmol) y carbonato de potasio (0.276 g, 2.0 mmol) La mezcla se calentó a 50 °C durante aprox. 20 horas, luego a 80 °C durante aprox. 4 horas. La mezcla se diluyó con EtOAc (50 mL) , se lavó con agua (30 mL + 15 mL x 2) y salmuera (20 mL) . Las capas organicas se recolectaron y concentraron. La cromatografía rápida proporcionó el compuesto del titulo (134 mg, 50%) . LC - MS m/z 538 $(M + H)^+$; ^1H - NMR (MeOD) δ 0.96 – 1.02 (m, 6 H) , 1.61 – 1.72 (m, 2 H) , 1.85 – 1.96 (m, 2 H) , 2.30 (s, 3 H) , 3.07 (q, J = 7.11 Hz, 2 H) , 3.19 – 3.29 (m, 3 H) , 3.33 – 3.40 (m, 3 H) , 3.83 (d, 1 H) , 3.90 (d, 1 H) , 6.83 – 6.99 (m, 3 H) , 7.51 (d, J = 8.03 Hz, 1 H) , 7.69 (d, J = 1.76 Hz, 1 H) , 7.87 (dd, J = 7.91, 1.88 Hz, 1 H) .

MÉTODOS DE TRATAMIENTO

Los compuestos de (I) y (Ia) , (II) y (IIa) , (III) y (IIIa) , (IV) y (IVa) , (V) y (Va) , (VI) , (VIa - VIi) , (VIII) y (VIIIa) , (IX) y (IXa) , (A) , (A1) , (B) , y (B1) , o una sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable de los mismos pueden ser usados en la producción de un medicamento para el tratamiento profiláctico o terapéutico de cualquier estado de enfermedad en un humano, u otro mamífero, que sea exacerbado o causado por la producción excesiva o no regulada de citoquinas por las células de tales mamíferos, como por ejemplo, pero no limitándose a monocitos y/o macrófagos.

Para fines del presente, los compuestos de las Fórmulas (I) y (Ia) , (II) y (IIa) , (III) y (IIIa) , (IV) y (IVa) , (V) y (Va) , (VI) , (VIa - VIi) , (VIII) y (VIIIa) , (IX) y (IXa) , (A) , (A1) , (B) , y (B1) , etc., todos serán considerados como compuestos de la Fórmula (I) en la presente a menos que se indique lo contrario.

Los compuestos de la Fórmula (I) son capaces de inhibir citoquinas proinflamatorias tales como IL - 1, IL - 6, IL - 8, y TNF y por lo tanto útiles en terapia. Las IL - 1, IL - 6, IL - 8, y TNF afectan una amplia variedad de células y tejidos y estas citoquinas, como también otras citoquinas derivadas a partir de leucocitos, son mediadores inflamatorios críticos e importantes de una amplia variedad de enfermedades y condiciones. La inhibición de dichas citoquinas pro - inflamatorias ofrece un beneficio para el control, la reducción y el alivio de muchos de estos estados patológicos.

Por lo tanto, el presente invento proporciona un método para el tratamiento de una enfermedad mediada por citoquinas el cual comprende la administración de una cantidad efectiva que interfiera con citoquinas de un compuesto de la Fórmula (I) o una sal farmacéutica aceptable del mismo.

Los compuestos de la Fórmula (I) son capaces de inhibir proteínas proinflamatorias inducibles, tales como la COX - 2, también conocidas por muchos otros nombres como por ejemplo la prostaglandina endoperóxido sintetasa - 2 (PGHS - 2) y por lo tanto útil en terapia. Estos mediadores lipídicos proinflamatorios de la vía ciclooxigenasa (CO) son producidos por la enzima inducible COX - 2. Por lo tanto, la regulación de COX - 2, responsable por estos productos derivados del ácido araquidónico tales como las prostaglandinas que afectan una amplia variedad de células y tejidos, son mediadores inflamatorios críticos e importantes en una amplia variedad de estados y condiciones patológicas. La expresión de COX - 1 no es afectada por compuestos de la Fórmula (I) . Esta inhibición selectiva de COX - 2 puede aliviar o perdonar la responsabilidad ulcerogénica asociada con la inhibición de COX - 1 por lo tanto inhibiendo las prostaglandinas esenciales para los efectos citoprotectores. Por lo tanto, la inhibición de estos mediadores pro - inflamatorios son de beneficio en el control, la reducción y el alivio

de muchos de dichos estados patológicos. De manera más particular, estos mediadores infamatorios, especialmente las prostaglandinas, han sido implicados en dolor, como por ejemplo en la sensibilización de receptores del dolor, o edema. Este aspecto del manejo de dolor por lo tanto incluye el tratamiento de dolor neuromuscular, cefalea, dolor asociado con cáncer, y dolor por artritis. Los compuestos de la Fórmula (I) o una sal farmacéuticamente aceptable, son útiles en la profilaxis o terapia en un humano, u otro mamífero, por la inhibición de la síntesis de la enzima COX - 2.

Así las cosas, el presente invento proporciona un método para inhibir la síntesis de la COX - 2 que comprende administrar una cantidad efectiva de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo. El presente invento también proporciona un método de tratamiento profiláctico en un humano, u otro mamífero, debido a la inhibición de la síntesis de la enzima COX - 2.

En particular, los compuestos de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo son útiles en la profilaxis o terapia de cualquier patología en un humano, u otro mamífero, que sea exacerbada o causada por la producción excesiva o no regulada de la producción de IL - 1, IL - 6, IL - 8, y TNF por la célula de tal mamífero, tales como, pero no limitándose a monocitos y/o macrófagos.

Por consiguiente, en otro aspecto, este invento se relaciona con un método de inhibir la producción de IL - 1 en un mamífero en necesidad del mismo el cual comprende la administración en dicho mamífero de una cantidad efectiva de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Existen muchos estados patológicos en donde la producción excesiva o no regulada de IL - 1 esté implicada en exacerbar y/o causar la enfermedad. Estos incluyen la artritis reumatoide, osteoartritis, meningitis, ACV isquémico o hemorrágico, neurotrauma o lesión de cráneo cerrado, ACV, endotoxemia y/o síndrome de choque tóxico, u otros estados patológicos inflamatorios crónicos o agudos tales como la reacción inflamatoria inducida por endotoxina o la enfermedad de intestino inflamado, tuberculosis, ateroesclerosis, degeneración muscular, esclerosis múltiple, caquexia, reabsorción ósea, artritis psoriática, síndrome de Reiter, gota, artritis traumática, artritis rubella y sinovitis aguda. Evidencia reciente también vincula la actividad de la IL - 1 a la diabetes, enfermedades pancreáticas de células β y enfermedad de Alzheimer.

El uso de un compuesto inhibidor CSAID para el tratamiento de estados patológicos mediados por CSBP, pueden incluir, pero no limitarse a enfermedades neurodegenerativas, tales como la enfermedad de Alzheimer (tal como se nombró anteriormente), enfermedad de Parkinson y esclerosis múltiple, etc.

En un aspecto adicional, este invento se relaciona con un método para inhibir la producción de TNF en un mamífero en necesidad de ello, el cual comprende administrarle a dicho mamífero una cantidad efectiva de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo.

La producción excesiva o no regulada de TNF (factor de necrosis tumoral) ha sido implicada en la mediación o exacerbación de un número de patologías que incluyen la artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa, y otras condiciones artríticas, sepsis, choque séptico, choque endotóxico, sepsis gram negativo, síndrome de choque tóxico, síndrome de distrés respiratorio adulto, enfermedad inflamatoria pulmonar crónica y EPOC, silicosis, sarcoisosis pulmonar, enfermedades por reabsorción ósea, tales como la osteoporosis, lesión por reperfusión cardiaca, cerebral y renal, reacción de injerto versus huésped, rechazos de aloinjertos, fiebre y mialgias debido a infección, tales como la influenza, infecciones cerebrales incluyendo la encefalitis (incluyendo formas inducidas por el VIH), malaria cerebral, meningitis, ACV isquémica o hemorrágica, caquexia secundaria a infección o malignidad, caquexia secundaria a SIDA, SIDA, complejo relacionado con el SIDA, formación de

queloide, formación de tejido cicatrizante, enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerativa, y piresis.

Los compuestos de la Fórmula (I) también son útiles en el tratamiento de las infecciones virales, en donde tales virus sea sensibles a regulación positiva por el FNT (TNF (*sigla en inglés*, factor de necrosis tumoral) o donde impulsen la producción de FNT en vivo. Los virus contemplados para el tratamiento en la presente son aquellos que producen FNT como resultado de una infección, o aquellos sensibles a la inhibición, como por ejemplo debido a una replicación disminuida, directa o indirectamente, por los compuestos inhibidores de FNT de la Fórmula (I). Tales virus incluyen, pero no se limitan a HIV - 1, HIV - 2, y HIV - 3, citomegalovirus (CMV), influenza, adenovirus y el grupo de virus de Herpes, tales como pero no limitados al Herpes Zoster y Herpes Simplex. Así, en un aspecto adicional, este invento se relaciona con un método para el tratamiento de un mamífero afligido con un HIV el cual comprende administrarle a tal mamífero una cantidad efectiva que inhiba el FNT de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo.

También se reconoce que tanto IL - 6 e IL - 8 son producidos durante infecciones por rinovirus (HRV) y contribuyen a la patogénesis del catarro común y la exacerbación del asma asociado con la infección por rinovirus (Turner et al. (1998), Clin. Infec. Dis., vol. 26, p 840; Teren et al. (1997), Am. J. Respir. Crit. Care Med., vol. 155, p 1362; Grunberg et al. (1997), Am. J. Respir. Crit. Care Med., vol. 156, p 609 y Zhu et al, J Clin. Invest (1996), 97:421). Se ha demostrado también in vitro que la infección de células pulmonares epiteliales con HRV resulta en la producción de IL - 6 e IL - 8 (Subauste et al., J. Clin. Invest. 1995, 96:549). Las células epiteliales representan el sitio primario de infección por HRV. Por lo tanto, otro aspecto del presente invento es un método de tratamiento para reducir la inflamación asociada con la infección por rinovirus, no necesariamente un efecto directo del virus como tal.

Los compuestos de la Fómula (I) también pueden ser usados en conjunto con el tratamiento veterinario de mamíferos, diferente a humanos, que necesiten de la inhibición de la producción del FNT. Las patologías mediadas por el FNT para el tratamiento, bien sea terapéuticamente o profilácticamente, en animales incluyen los estados patológicos como los anteriores, pero en particular las infecciones virales. Ejemplos de tales virus incluyen, pero no están limitados a infecciones por lentivirus tales como el virus de anemia infecciosa equina, virus de artritis caprina, virus visna, o infecciones por retrovirus o virus maedi, tales como pero no limitándose al virus de inmunodeficiencia felina (FIV), virus de inmunodeficiencia bovina, o virus de inmunodeficiencia canina u otras infecciones retrovirales.

Los compuestos de la Fórmula (I) también pueden usarse de manera tópica en el tratamiento o profilaxis de estados patológicos tópicos mediados por o exacerbados por la producción excesiva de citoquinas, tales como por IL - 1 o FNT respectivamente, como por ejemplos articulaciones inflamadas, eczema, soriasis y otras condiciones dermatológicas inflamatorias tales como quemaduras por rayos solares; condiciones oculares inflamatorias incluyendo la conjuntivitis; piresis, dolor y otras condiciones asociadas con la inflamación. La enfermedad periodóntica también ha sido implementada en la producción de citoquinas, tanto tópicamente como sistémicamente. Por lo tanto, el uso de compuestos de la Fórmula (I) para el control de la inflamación asociada con la producción de citoquinas en tales patologías perorales tales como la gingivitis y periodontitis es otro aspecto del presente invento.

Los compuestos de la Fórmula (I) también han comprobado en inhibir la producción de IL - 8 (Interleukina - 8, NAP). Así, en un aspecto adicional, este invento se relaciona con un método para inhibir la producción de IL - 8 en un mamífero en necesidad de ello el cual comprende la administración a dicho mamífero una cantidad efectiva de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Existen muchos estados patológicos en donde la producción excesiva o no regulada de IL - 8 está implicada en la exacerbación y/o causa de la enfermedad. Esta patologías son caracterizadas por la infiltración masiva de neutrófilos tales como soriasis, enfermedad inflamatoria del intestino, asma, lesión por repercusión cardiaca, cerebral y renal, síndrome de distrés respiratorio adulto, trombosis, y glomerulonefretis. Todas estas enfermedades están asociadas con la producción aumentada de IL - 8 el cual es responsable por la quimiotaxis de neutrófilos al sitio de inflamación. En contraste a otras citoquinas inflamatorias (IL - 1, FNT, e IL - 6) , IL - 8 posee la propiedad única de promover la quimiotaxis y activación de neutrófilos.

Los compuestos de la Fórmula (I) se administran en una cantidad suficiente para inhibir la producción de citoquinas, en particular IL - 1, IL - 6, IL - 8 o FNT de tal manera que se regule negativamente a niveles normales, o en algunos casos a niveles subnormales, con el fin de aminorar o prevenir el estado patológico. Los niveles anormales de IL - 1, IL - 6, IL - 8 o FNT por ejemplo, en el contexto del presente invento, constituyen: (i) niveles de IL - 1, IL - 6, IL - 8 o FNT libres (no ligados a células) mayores o igual a 1 picogramo por mililitro; (ii) cualquier célula asociada con IL - 1, IL - 6, IL - 8 o FNT; ó (iii) la presencia de ARNm de IL - 1, IL - 6, IL - 8 o FNT por encima de niveles basales en células o tejidos en donde IL - 1, IL - 6, IL - 8 o FNT, respectivamente, sea producido.

El descubrimiento que los compuestos de la Fórmula (I) sean inhibidores de citoquinas, específicamente IL - 1, IL - 6, IL - 8 o FNT se basa en los efectos de los compuestos de las Fórmulas (I) sobre la producción de IL - 1, IL - 8 y FNT en ensayos en vitro los cuales se describen en la presente.

Tal como se utiliza en la presente, el término "inhibir la producción de IL - 1 (IL - 6, IL - 8 o FNT) " se refiere a:

a) una reducción de niveles excesivos en vivo de la citoquina (IL - 1, IL - 6, IL - 8 o FNT) en un humano a niveles normales o sub - normales mediante la inhibición de la liberación *in* de la citoquina por todas las células, incluyendo pero no limitándose a monocitos o macrófagos;

b) una regulación negativa, a nivel genómico, de niveles excesivos en vivo de la citoquina (IL - 1, IL - 6, IL - 8 o FNT) en un humano a niveles normales o sub - normales;

c) una regulación negativa, mediante una inhibición de la síntesis directa de la citoquina (IL - 1, IL - 6, IL - 8 o FNT) como evento pos - traducción; ó

d) una regulación negativa, a nivel de traducción, de niveles excesivos en vivo de la citoquina (IL - 1, IL - 6, IL - 8 o FNT) en un humano a niveles normales o sub - normales.

Tal como se utiliza en la presente, el término "enfermedad o estado patológico mediado por el FNT" se refiere a cualquier o todos los estados patológicos en donde el FNT juega un papel, bien sea por la producción de FNT por si solo, o porque el FNT causa que otra monoquina se libere, como por ejemplo pero no limitándose a IL - 1, IL - 6, u IL - 8. Por lo tanto se consideraría un estado patológico mediado por el FNT el cual la IL - 1 fuera un componente principal y cuya producción o acción fuera exacerbada o secretada en respuesta al FNT.

Según se utiliza en la presente, el término "citoquina" se refiere a cualquier polipéptido secretado que afecte las funciones de las células y es una molécula que modula las interacciones entre células en la respuesta inmune, inflamatoria, o hematopoyética. Una citoquina incluye, pero no se limita a monquinas y linfoquinas, sin importar cuáles células las producen. Por ejemplo, la monoquina generalmente es aquella producida y secretada por una célula mononuclear, como por ejemplo un macrófago y/o monocito. Sin embargo muchas otras células también producen monoquinas, como las células asesinas, fibroblastos, basófilos, neutrófilos, células endoteliales, astrocitos del SNC, células estromales de la médula ósea, queratinocitos epiderales y B - linfocitos. Las linfoquinas generalmente son aquellas producidas por los

linfocitos. Ejemplos de citoquinas incluyen pero no se limitan a la IL - 1, IL - 6, IL - 8, FNT - α y el FNT - β.

Tal como se utiliza en la presente, el término "que interfiere con las citoquinas" o "cantidad supresora de citoquinas" se refiere a una cantidad efectiva de un compuesto de la Fórmula (I) la cual causará una disminución de los niveles en vivo de la citoquina a niveles normales o sub - normales al administrarse a un paciente para la profilaxis o tratamiento de una enfermedad la cual es exacerbada por, o causada por la producción excesiva o no regulada de citoquinas.

Tal como se utiliza en la presente, la citoquina a la cual se refieren en la frase "inhibición de una citoquina, para uso en el tratamiento de un humano infectado por VIH" es una citoquina la cual está implicada en (a) la iniciación y/o mantenimiento de la activación de células T y/o expresión génica de VIH mediado por células T y/o replicación y/o (b) cualquier problema asociado con una patología mediada por citoquinas tales como la caquexia o la degeneración muscular.

Puesto que el FNT - β (también conocido como la linfotoxina) tiene una estrecha homología estructural con el FNT - α (también conocido como caquectina) y puesto que cada uno induce respuestas biológicas similares y se unen al mismo receptor celular, tanto el FNT - α como el FNT - β son inhibidos por los compuestos del presente invento y por lo tanto son referidos colectivamente en la presente como "FNT" a menos que se especifique de lo contrario.

Un miembro de la familia de las quinasas MAP, llamadas de manera alterna CSBP, p38, o RK, ha sido identificado de manera independiente por varios laboratorios. La activación de esta proteinquinasa novedosa por vía de una fosforilación dual ha sido observada en diferentes sistemas celulares al someterse a una estimulación por un amplio espectro de estímulos, como por ejemplo estrés fisicoquímico y tratamiento con lipopolisacáridos o citoquinas proinflamatorias tales como la IL - 1 y el factor de necrosis tumoral. Los compuestos inhibidores de la biosíntesis de citoquinas de la Fórmula (I) , del presente invento, han sido determinados en ser inhibidores potentes y selectivos de la actividad de la quinasa CSBP/p38/RK. Se ha encontrado que algunos de los compuestos de la Fórmula I exhiben una inhibición reversible dependiente del tiempo de la quinasa p38 debido a la cinética de unión lenta y/o disociación lenta, resultando en un mejorado IC50 aparente cuando un compuesto ha sido preincubado con la enzima o con las células. Esta propiedad lenta y de unión estrecha podría contribuir con la potencia mejorada de tales compuestos tanto en vitro y en vivo.

Estos inhibidores son de mucha ayuda al determinar cómo las vías de señales se involucran en las respuestas inflamatorias. En particular, por primera vez una vía de transducción de señal definitiva pudo asignarse a la acción de lipopolisacáridos en la producción de citoquinas en los macrófagos. Además de aquellas enfermedades ya enumeradas, también pueden incluirse el tratamiento de ACVs, neurotrauma, lesión por reperfusión cardiaca y renal, falla cardiaca congestiva, cirugía de injerto *bypass* de arterias coronarias, falla renal crónica, angiogénesis y procesos relacionados, tales como el cáncer, trombosis, glomerulonefritis, diabetes y células β pancreáticas, esclerosis múltiple, degeneración muscular, eczema, soriasis, quemadura por rayos solares, y conjuntivitis.

Los inhibidores de CSBP fueron luego probados en un número de modelos animales buscando actividad anti - inflamatoria. Se escogieron sistemas de modelos que fueran relativamente insensibles a los inhibidores de la ciclooxigenasa con el fin de divulgar las actividades únicas de los agentes supresores de citoquinas. Los inhibidores exhibieron una actividad significativa en muchos de aquellos estudios en vivo. Lo más notable fue su efectividad en el modelo de artritis inducida por colágeno y la inhibición de la producción del FNT en el modelo de choque endotóxico. En el estudio posterior, la reducción en el nivel de FNT en plasma correlacionaba con supervivencia y protección contra mortalidad relacionada con choque endotóxico. También de gran importancia es la efectividad del compuesto en inhibir la reabsorción ósea en un sistema de cultivo de órganos óseos largos de fetos de rata. Griswold et al.,

(1988) Arthritis Rheum. 31:1406 - 1412; Badger, et al., (1989) Circ. Shock 27, 51 - 61; Votta et al., (1994) in vitro. Bone 15, 533 - 538; Lee et al., (1993) . B Ann. N.Y. Acad. Sci. 696, 149 - 170.

Enfermedades crónicas que tienen un componente angiogénico inadecuado son varias neovascularizaciones oculares, tales como la retinopatía diabética y la degeneración macular. Otras patologías crónicas que tengan una proliferación excesiva o aumentada de la vasculatura son el crecimiento tumoral y la metástasis, ateroesclerosis, y ciertas condiciones artríticas. Por lo tanto, los inhibidores de la quinasa CSBP serán útiles en el bloqueo del componente angiogénico de estos estados patológicos.

El término "proliferación excesiva o aumentada de la angiogénesis inadecuada de la vasculatura" tal cual se usa en la presente incluye, pero no está limitado a patologías caracterizadas por hemangiomas y patologías oculares.

El término "angiogénesis inadecuada" tal cual se usa aquí incluye pero no se limita a enfermedades caracterizadas por la proliferación de vesículas con una proliferación de tejidos acompañantes, tal cual ocurre con el cáncer, metástasis, artritis y ateroesclerosis.

Así las cosas, el presente invento proporciona un método para tratar una enfermedad mediada por la quinasa CSBP en un mamífero en necesidad de ello, preferiblemente un humano, el cual comprende administrarle a dicho mamífero una cantidad efectiva de un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo.

Con el propósito de usar un compuesto de la Fórmula (I) o una sal farmacéuticamente aceptable del mismo en terapia, normalmente será formulado en una composición farmacéutica según la práctica farmacéutica estándar. Por lo tanto, este invento también se relaciona con una composición farmacéutica que comprende una cantidad efectiva no tóxica de un compuesto de la Fórmula (I) y un vehículo o diluyente farmacéuticamente aceptable.

Los compuestos de la Fórmula (I) , sales farmacéuticamente aceptables de los mismos y composiciones farmacéuticas que incorporan tales compuestos y sales pueden ser administradas de manera conveniente por cualquiera de las vías convencionalmente usadas para la administración de fármacos, como por ejemplo oralmente, tópicamente, parenteralmente, o mediante inhalación. Los compuestos de la Fórmula (I) pueden administrarse en formas de dosificación convencionales preparadas al combinar un compuesto de la Fórmula (I) con vehículos farmacéuticos estándares según procedimientos convencionales. Los compuestos de la Fórmula (I) también pueden administrarse en dosificaciones convencionales en combinación con un segundo compuesto terapéuticamente activo conocido. Estos procedimientos pueden involucrar el mezclado, granulado y compresión o disolución de los ingredientes según lo adecuado para la preparación deseada. Será apreciado que la forma y carácter del vehículo o diluyente farmacéuticamente aceptable es dictado por la cantidad de ingrediente activo con el cual debe ser combinado, la vía de administración y otras variables bien conocidas. Los vehículos deben ser "aceptables" en relación a que deben ser compatibles con los otros ingredientes de la formulación y no nocivo al recipiente del mismo.

Por ejemplo, el vehículo farmacéutico empleado puede ser bien sea un sólido o un líquido. Ejemplos de vehículos sólidos son la lactosa, terra alba, sacarosa, talco, gelatina, agar, pectina, acacia, estearato de magnesio, ácido esteárico, y similares. Ejemplos de vehículos líquidos son el jarabe, aceite de maní, aceite de oliva, agua y similares. De manera similar, el vehículo o diluyente puede incluir material de retrazo de tiempo bastante conocido en el estado de la técnica, como lo es el mono - estearato de glicerilo o diestearato de glicerilo por sí solo o con una cera.

Una amplia variedad de formas farmacéuticas pueden emplearse. Por ende, si se usa un vehículo sólido, la preparación puede entabletarse, colocarse dentro de una cápsula de gelatina dura en forma de

polvo o pellets o en forma de un trocisco o pastilla. La cantidad de vehículo sólido variará de manera amplia pero preferiblemente oscilará entre 25 mg y 1 gramo aproximadamente. Cuando se use un vehículo liquido, la preparación será en forma de un jarabe, emulsión, cápsula de gelatina suave, líquido inyectable estéril como por ejemplo una ampolla o suspensión líquida no acuosa.

Los compuestos de la Fórmula (I) pueden administrarse de manera tópica, es decir mediante administración o sistémica. Esto incluye la aplicación de un compuesto de la Fórmula (I) de manera externa a la epidermis o la cavidad bucal y la instilación de tal compuesto dentro del oído, ojo o nariz, para que de tal manera el compuesto no ingrese de manera significativa al torrente sanguíneo. En contraste, la administración sistémica se refiere a la vía oral, intravenosa, intraperitonea, e intramuscular.

Las formulaciones adecuadas para la administración tópica incluyen preparaciones líquidas o semi - líquidas adecuadas para la penetración a través de la piel hacia el sitio de inflamación como por ejemplo linimientos, lociones, cremas, ungüentos, o pastas, y gotas adecuadas para administrarse en el ojo, oído o nariz. El ingrediente activo puede comprender, para la administración tópica, entre 0,001% y 10% peso/peso, por ejemplo entre 1% y 2% por peso de la formulación. Sin embargo, puede comprender hasta un 10% peso/peso pero preferiblemente comprenderá menos del 5% peso/peso, y de manera más preferible entre 0,1% y 1% peso/peso de la formulación.

Las lociones según el presente invento incluyen aquellas adecuadas para su aplicación sobre la piel o dentro del ojo. Una loción oftalmológica puede comprender una solución acuosa estéril que contiene un bactericida y puede prepararse con métodos similares a aquellos para la preparación de gotas. Las lociones y linimentos para aplicación en piel también podrán incluir un agente para acelerar el secado y para refrescar la piel, como por ejemplo el alcohol o acetona, y/o un humectante como por ejemplo glicerol o un aceite como el aceite de ricino o el aceite de arachis.

Las cremas, ungüentos o pastas según el presente invento son formulaciones semi - sólidas del ingrediente activo para aplicación externa. Pueden ser preparadas al mezclar el ingrediente activo en forma de polvo o finamente dividido, por si solo o en solución o suspensión en un fluido acuoso o no acuoso, con la ayuda de maquinaria adecuada, con una base aceitosa o no aceitosa. La base puede comprender hidrocarbonos como por ejemplo parafina dura, suave o líquida, glicerol, cera de abejas, un jabín metálico; un mucílago; un aceite de origen natural como por ejemplo aceite de almendras, maíz, arachis, ricino o oliva; grasa de lana o sus derivados o un ácido graso como el ácido esteárico u oleico junto con un alcohol como el glicol de propileno o un macrogel. La formulación puede incorporar cualquier agente de tensión superficial adecuado como por ejemplo un surfactante aniónico, catiónico o no - iónico como el éster de sorbitán o un derivado de polioxietileno del mismo. Agentes de suspensión tales como gomas naturales, derivados de celulosa o materiales inorgánicos tales como la sílices silicáceas, u otros ingredientes como la lanolina, también pueden incluirse.

Según el presente invento, las gotas pueden comprender soluciones o suspensiones estériles acuosas o aceitosas y pueden prepararse al disolver el ingrediente activo en una solución acuosa adecuada de un agente bactericida y/o fungicida y/o cualquier otro preservativo adecuado, y preferiblemente incluyendo un agente de tensión superficial. La solución resultante puede luego ser clarificada mediante filtración, transferida a un recipiente adecuado el cual luego es sellado y esterilizado en autoclave o mantenido a 90 - 100°C por media hora. De manera alternativa, la solución puede esterilizarse por medio de filtración y transferida al recipiente por medio de una técnica aséptica. Ejemplos de agentes bactericidas o fungicidas adecuados para incluirse en las gotas son el nitrato o acetato fenilmercúrico (0,002%), cloruro de benzalconio (0,01%) y el acetato de clorhexidina (0,01%). Solventes adecuados para la preparación de una solución aceitosa incluyen el glicerol, alcohol diluido y glicol de propileno.

Los compuestos de la Fórmula (I) pueden administrarse de manera parenteral, es decir de manera intravenosa, intramuscular, subcutánea, intranasal, intrarectal, intravaginal, o intraperitonea. Las formas

subcutáneas e intramusculares de administración parenteral generalmente son preferidas. Formas de dosificación adecuadas para tal administración pueden prepararse mediante técnicas convencionales. Los compuestos de la Fórmula (I) también pueden administrarse mediante inhalación, es decir por administración intranasal o inhalación oral. Formas de dosificación adecuadas para tal administración, tales como una formulación en aerosol o un inhalador de dosis medida pueden prepararse utilizando técnicas convencionales.

En una realización del presente invento, los agentes del presente invento son distribuidos vía inhalación oral o administración intranasal. Formas de dosificación adecuadas para tal administración, tales como una formulación en aerosol o un inhalador de dosis medida pueden prepararse utilizando técnicas convencionales.

Para la administración por inhalación, los compuestos pueden distribuirse e forma de una presentación de atomización en aerosol a partir de empaques presurizados o un nebulizador, con el uso de un propelente adecuado, por ejemplo el diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, un hidrofluoroalcano como por ejemplo el tetrafluoroetano o heptafluoropropano, dióxido de carbono u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación puede determinarse al proporcionar una válvula para distribuir una cantidad medida. Las cápsulas o cartuchos de por ejemplo la gelatina para uso en un inhalador o insuflador pueden formularse de manera que contengan una mezcla de polvos de un compuesto del invento y una base de polvo adecuada como lo es por ejemplo la lactosa o el almidón.

Las composiciones de polvo seco para distribución tópica al pulmón mediante inhalación pueden, por ejemplo, estar presentadas en cápsulas o cartuchos de por ejemplo gelatina o blisters de papel de aluminio laminado, para uso en un inhalador o insuflador. Las formulaciones de mezcla de polvos generalmente contienen una mezcla de polvos para inhalación del compuesto del invento y una base de polvo adecuada (vehículo/diluyente/excipiente) como por ejemplo mono - , di - , o poli - sacáridos (por ejemplo, lactosa o almidón) . El uso de la lactosa es preferida.

Cada cápsula o cartucho pueden generalmente contener entre 20μg y 10 mg del compuesto de la Fórmula (I) opcionalmente en combinación con otro ingrediente terapéuticamente activo. De manera alterna, el compuesto del invento puede estar en una presentación sin excipientes.

De manera adecuada, el dispensador de empaque/medicamento es de un tipo seleccionado a partir de un grupo que consiste de un inhalador de polvo seco en reservorio (RDPI) , un inhalador de polvo seco de múltiples dosis (MDPI) , y un inhalador de dosis medidas (MDI) .

Por inhalador de polvo seco en reservorio (RDPI) se quiere decir que es un inhalador con un reservorio para dosis múltiples no medidas del medicamento en forma de polvo seco e incluyendo un medio para medir la dosis de medicamento a partir del reservorio hacia una posición de distribución. El medio de medición puede ser por ejemplo una taza medidora, la cual es movible desde una primera posición donde la taza puede ser llenada con el medicamento a partir del reservorio hasta una segunda posición en donde la dosis de medicamento medida está disponible al paciente para su inhalación.

Por inhalador de polvo seco de múltiples dosis (MDPI) se quiere decir un inhalador adecuado para dispensar medicamento en forma de polvo seco, en donde el medicamento se encuentra dentro de un empaque de múltiples dosis que contiene (o de lo contrario lleva) dosis múltiples y definidas (o partes de las mismas) del medicamento. En un aspecto preferido, el vehículo tiene una forma de empaque blister, pero podría también por ejemplo, comprender un empaque con base en cápsulas o un vehículo sobre el cual ha sido aplicado el medicamento por cualquier proceso adecuado incluyendo impresión, pintura y oclusión al vacío.

En el caso de distribución de múltiples dosis, la formulación puede ser previamente medida (por ejemplo en Diskus, ver las patentes GB 2242134, US 6.632.666, 5.860.419, 5.873.360 y 5.590.645 o el Diskhaler, ver la GB 2178965 y 2169265, US 4.778.054, 4.811.731, 5.035.237, divulgaciones de las cuales están incorporadas en la presente como referencia) o medida durante el uso. Un ejemplo de un dispositivo de dosis unitaria es el Rotahaler (ver la GB 2064336 y la US 4.353.656, divulgaciones de las cuales están incorporadas en la presente como referencia) .

El dispositivo de inhalación Diskus comprende una tira alongada formada a partir de una hoja base con una pluralidad de depresiones espaciadas a lo largo y una hoja de tapa sellada de manera hermética pero que puede pelarse para retirar y así definir una pluralidad de recipientes, cada uno conteniendo una formulación que puede inhalarse que contiene un compuesto de la fórmula (I) ó (Ia) preferiblemente combinado con lactosa. Preferiblemente, la tira es lo suficientemente flexible para enrollarse. La hoja de tapa y la hoja base preferiblemente tendrían porciones de extremo guía no selladas entre sí y por lo menos una de dichas porciones de extremo guía es hecha de manera que está unida a un medio de enrollado. Igualmente, preferiblemente el sello hermético entre las hojas tapa y base se extiende sobre todo su ancho. La hoja tapa puede preferiblemente ser pelada de la hoja base en dirección longitudinal a partir de un primer extremo de dicha hoja base.

En un aspecto, el empaque de múltiples dosis es un empaque blister que comprende múltiples blisteres para contener el medicamento en forma de polvo seco. Los blisters típicamente son ordenados de manera regular para facilitar la liberación del medicamento.

En un aspecto, el empaque de múltiples dosis comprende una pluralidad de blisteres ordenados de manera circular sobre un empaque blister en forma de disco. En otro aspecto, el empaque blister de múltiples dosis tiene una forma alongada, por ejemplo comprendiendo una tira o una cinta.

En un aspecto, el empaque blister de múltiples dosis es definido entre dos miembros asegurados de manera pelable o rasgable entre sí. Las patentes US 5.860.419, 5.873.360, y 5.590.645 describen empaque de medicamento de este tipo general. En este aspecto, el dispositivo es usualmente proporcionado con una estación de apertura que comprende un medio de pelado o rasgado para apartar los miembros por medio de una acción de pelar y así acceder a cada dosis de medicamento. De manera adecuada, el dispositivo es adaptado para usarse donde los miembros pelables son hojas alongadas que definen una pluralidad de recipientes para medicamentos espaciados a lo largo del mismo, el dispositivo estando proporcionado con medios indexadores para así indexar cada recipiente. De manera más preferible, el dispositivo es adaptado para usarse cuando una de las hojas es una hoja base con una pluralidad de bolsillos en ella, y la otra hoja es una hoja tapa, cada bolsillo y la parte adyacente de la hoja tapa definiendo un recipiente respectivo, el dispositivo comprende medios de impulso para jalar la hoja tapa de la hoja base a la altura de la estación de apertura.

Por inhalador de dosis medida (MDI) se quiere decir que es un dispensador de medicamentos adecuado para dispensar medicamentos en forma aerosol, en donde el medicamento se encuentra dentro de un recipiente de aerosol adecuado para contener una formulación de medicamento en aerosol con base en propelentes. El recipiente de aerosol típicamente se proporciona con una válvula de medición, como por ejemplo una válvula deslizante, para la liberación de la formulación del medicamento en forma de aerosol hacia el paciente. El recipiente de aerosol generalmente está diseñado para distribuir una dosis de medicamento predeterminada después de cada activación por medio de una válvula, la cual puede abrirse al oprimir la válvula mientras se mantiene el recipiente estacionario o al oprimir el recipiente mientras que la válvula queda estacionaria.

En el caso donde el recipiente de medicamentos es un recipiente de aerosol, la válvula típicamente comprende un cuerpo de válvula con un puerto de entrada a través del cual una formulación del medicamento en aerosol puede ingresar a dicho cuerpo de válvula, un puerto de salida a través del cual el

aerosol puede salir del cuerpo de válvula y un mecanismo de apertura/cierre por medio del cual el flujo a través de dicho puerto de salida es controlable.

La válvula puede ser una válvula deslizante en donde el mecanismo de apertura/cierre comprende un anillo de sellamiento y que recibe desde el anillo de sellamiento un eje de válvula con un pasaje dispensador, el eje de válvula siendo móvil de manera deslizable dentro del anillo desde una posición de válvula cerrada hasta una posición de válvula abierta en donde el interior del cuerpo de válvula está en comunicación con el exterior del cuerpo de válvula por medio del pasaje dispensador.

Típicamente, la válvula es una válvula medidora. Los volúmenes de medición típicamente oscilan entre 10 y 100µl, como por ejemplo 25 µl, 50 µl, ó 63 µl. De manera adecuada, el cuerpo de válvula define una cámara de medición para la medición de una cantidad de formulación de medicamento y un mecanismo de apertura/cierre por medio del cual el flujo a través del puerto de entrada hacia la cámara de medición es controlable. Preferiblemente, el cuerpo de válvula tiene una cámara de muestreo en comunicación con la cámara de medición vía un segundo puerto de entrada, dicho puerto de entrada es controlable por medio de un mecanismo de apertura/cierre por lo tanto regulando el flujo de la formulación del medicamento hacia la cámara de medición.

La válvula también podrá comprender una 'válvula de aerosol de flujo libre' con una cámara y un eje de válvula extendiéndose hacia la cámara y móvil con relación a la cámara entre posiciones dispensadoras y no dispensadoras. El eje de válvula posee una configuración y la cámara tiene una configuración interna de tal manera que un volumen medido es definido entre ellos y de tal manera que durante el movimiento entre las posiciones dispensadoras y no dispensadoras, el eje de válvula de manera secuencial: (i) permite el libre flujo de la formulación en aerosol hacia la cámara, (ii) define un volumen medido cerrado para la formulación en aerosol presurizado entre la superficie externa del eje de válvula y la superficie interna de la cámara, y (iii) se mueve con el volumen medido cerrado dentro de la cámara sin reducir el volumen del volumen medido cerrado hasta que el volumen medido se comunique con un pasaje de salida y por lo tanto permitiendo la dispensación del volumen medido de la formulación en aerosol presurizado. Una válvula de este tipo está descrita en la patente US 5.772.085. Adicionalmente, la distribución intra - nasal es efectiva de los presentes compuestos.

Para formular una composición nasal farmacéutica efectiva, el medicamento debe ser distribuido fácilmente a todas las zonas de las cavidades nasales (los tejidos objetivos) donde desarrolla su función farmacológica. Adicionalmente, el medicamento debe permanecer en contacto con los tejidos objetivos por períodos de tiempo relativamente prolongados. Cuanto más permanezca el medicamento en contacto con los tejidos objetivos, el medicamento deberá ser capaz de resistir aquellas fuerzas en los pasajes nasales que funcionan en remover partículas de la nariz. Tales fuerzas, a las cuales se refieren como 'depuración mucociliar' son reconocidas como extremadamente efectivas en remover partículas de la nariz de manera rápida, por ejemplo, en cuestión de 10 a 30 minutos desde el momento en que las partículas ingresen en la nariz.

Otras características deseadas para una composición nasal es que no debe contener ingredientes que causen una falta de confort al usuario, que tenga una estabilidad y propiedades de almacenamiento satisfactorias, y que no incluya elementos considerados nocivos para el ambiente, como por ejemplo, reductores de ozono.

Un régimen de dosificación adecuado para la formulación del presente invento al administrarse en la nariz sería que el paciente inhale profundamente luego de limpiarse bien la cavidad nasal. Durante la inhalación, la formulación sería aplicada en una narina mientras que la otra permanece oprimida. Este procedimiento luego se repetiría para la otra narina.

En una realización, el medio para la aplicación de una formulación del presente invento a los pasajes nasales es mediante el uso de una bomba de pre - compresión. De manera preferible, la bomba de pre - compresión sería un modelo VP7 fabricada por Valois S.A. Tal bomba es benéfica puesto que asegurará que la formulación no sea liberada hasta no aplicarse una fuerza suficiente, o de lo contrario pueden aplicarse dosis más pequeñas. Otra ventaja de la bomba de pre - compresión es que se asegura la atomización del atomizador puesto que no liberará la formulación hasta no lograr la presión de umbral para atomizar de manera efectiva el atomizador. Típicamente, el modelo VP7 puede usarse con una botella capaz de retener entre 10 y 50 ml de una formulación. Cada atomizador distribuirá típicamente entre 50 y 100 µl de tal formulación, y por lo tanto, el modelo VP7 es capaz de proporcionar por lo menos 100 dosificaciones medidas.

Las composiciones atomizadas para distribución tópica en el pulmón mediante inhalación pueden por ejemplo ser formuladas como soluciones o suspensiones acuosas o como aerosoles distribuidos a partir de empaques presurizados, como por ejemplo un inhalador de dosis medida, con el uso de un propelente licuado adecuado. Las composiciones en aerosol adecuadas para inhalación pueden ser bien sea una suspensión o una solución y generalmente contienen el compuesto de la Fórmula (I) opcionalmente en combinación con otro ingrediente terapéuticamente activo y un propelente adecuado como por ejemplo un fluorocarbono o clorofluorocarbono que contenga hidrógeno o mezclas de los mismos, particularmente los hidrofluoroalcanos, por ejemplo el diclorodifluorometano, triclorofluorometano, diclorotetra - fluoroetano, especialmente el 1,1,1,2 - tetrafluoroetano, 1,1,1,2,3,3,3 - heptafluoro - n - propano o una mezcla de los mismos. El dióxido de carbono u otro gas adecuado también puede ser usado como propelente. La composición en aerosol puede estar libre de excipientes o podrá contener de manera opcional excipientes de formulación adicional bastante conocidos en el estado de la técnica como lo son los surfactantes, por ejemplo, el ácido oleico o lecitina y cosolventes, por ejemplo el etanol. Las formulaciones presurizadas generalmente se retendrán en un recipiente (por ejemplo un recipiente de aluminio) cerrado con una válvula (por ejemplo una válvula medidora) y colocado en un activador proporcionado con una pieza bucal.

Los medicamentos para la administración por inhalación deseablemente tienen un tamaño de partícula controlada. El tamaño de partícula óptima para inhalación dentro del sistema bronquial es usualmente 1 a 10 µm, preferiblemente 2 a 5 µm. Aquellas partículas con un tamaño por encima de 20 µm generalmente son muy grandes al inhalarse para lograr llegar a las vías aéreas pequeñas. Para lograr estos tamaños de partícula, las partículas del ingrediente activo tal cual se producen podrán reducirse mediante medios convencionales, como por ejemplo por medio de una micronización. La fracción deseada podrá ser separada por clasificación aérea o por tamizaje. De manera apropiada, las partículas serán cristalinas en forma. Cuando un excipiente como la lactosa es usada, generalmente, el tamaño de partícula del excipiente será mucho mayor comparado con el medicamento inhalado del presente invento. Cuando el excipiente es lactosa, típicamente estará presente como lactosa molida, en donde no más del 85% de las partículas de lactosa tendrán un MMD de 60 y hasta 90 µm y no menos del 15% tendrán un MMD inferior a 15 µm.

Las atomizaciones intranasales puede formularse usando vehículos acuosos o no acuosos con la adición de agentes tales como agentes espesantes, sales buffer o ácidos o alcalinos para ajustar el pH, agentes ajustadores de la isotonicidad o anti - oxidantes.

Las soluciones para inhalación por nebulización pueden formularse con un vehículo acuoso con la adición de agentes tales como ácidos o alcalinos, sales buffer, agentes ajustadores de isotonicidad o antimicrobianos. Pueden esterilizarse mediante filtración o calentamiento en un autoclave, o presentados como un producto no estéril.

El invento ahora será descrito mediante referencia a los siguientes ejemplos biológicos los cuales son meramente ilustrativos y no deben considerarse como una limitación del alcance del presente invento.

EJEMPLOS BIOLÓGICOS

Los efectos inhibidores de la citoquina de los compuestos del presente invento puede determinarse por los siguientes análisis *in vitro:*

Los análisis para la interleukina - 1 (IL - 1beta), interleukina - 8 (IL - 8) y el factor de necrosis de tumor (TNTalfa) son bien conocidos en el arte, y pueden encontrarse en un número de publicaciones y patentes. Análisis representativos adecuados para su uso son descritos en Adams y colaboradores US 5,593,992 cuya divulgación se incorpora aquí completamente por referencia.

Interleukina - 1 (IL - 1)

Los monocitos de la sangre periférica humana se aislan y purifican ya sea de preparaciones de sangre frescas de donantes voluntarios o de capas leuco plaquetarias, de acuerdo al procedimiento de Colotta y colaboradores, J. Immunol, 132, 936 (1984), u otros procedimientos adecuados como la selección positiva usando cuentas MACS CD14+. Estos monocitos ($1x10^6$) se sirven en placas de 24, 48, 96 o 384 celdas a concentraciones de 1 - 2 millones/ml por celda. Se permite que las células se adhieran por 2 horas, después de las cuales las células no adheridas pueden removerse por un lavado suave. Los compuestos prueba se adicionan entonces a las células por 1h antes de la adición de polisacáridos (50 - 200 ng/ml) y los cultivos se incuban a 37°C por 24h adicionales. Al final del periodo, los sobrenadantes del cultivo se incuban a 37°C por 24h adicionales. Al final de éste periodo, los sobrenadantes del cultivo se remueven y clarifican de células y todos los todos los residuos. Los niveles de IL - 1 beta en el sobrenadante libre de células son determinados luego por análisis inmunoenzimático (ELISA) y otros procedimientos basados en anticuerpos.

Análisis de TNF *in vivo*

(1) Griswold et al, Drugs Ander exp. and clinical res. XIX (6) 243 - 248 (1993) o
(2) Boehm et al, Journal of medicinal chemistry 39, 3929 - 3937 (1996) cuyas revelaciones se incorporan aquí por referencia completamente.

Producción de TNFα inducida por LPS en ratones y ratas

Para evaluar inhibición in vivo de producción de TNFα en roedores, se inyectaron ratones o ratas con LPS.

Método de ratones

Ratones Balb/c machos de los laboratorios Charles River son pretratados (30 minutos) con el compuesto o el vehículo. Luego de 30 minutos de tiempo pretratamiento, se les dio a los ratores LPS (lipopolisacárido de Escherichia coli serotipo 055 - B5, químico sigma Co, St. Louis, MO) 25 µg/ratón en 25 µl de fosfato amortiguado salino (pH 7.0) intraperitonealmente. Dos horas más tarde los ratones se mataron por inhalación de CO2 y las muestras sanguíneas se recolectaron por sangrado en tubos recolectores heparinizados y almacenados en hielo. Las muestras de sangre se centrifugan y el plasma recolectado y almacenado a - 20°C hasta que se analizan para TNFα por ELISA.

Método de ratas

Las ratas macho Lewis de los laboratorios Charles Rives se pretrataron por varios periodos con compuesto o vehículo. Luego de un periodo determinado de pretratamiento, a las ratas se les suministró LPS (lipopolisacárido de Escherichia coli serotipo 055 - B5, Sigma chemical Co, St. Louis, MO) 3.0 mg/kg intraperitoneal. Las ratas se matan por inhalación de CO2 y la sangre total heparinizada se recolectó de cada rata por punción cardiaca 90 minutos luego de la inyección de LPS. Las muestras sanguíneas se centrifugan y el plasma recolectado para análisis por ELISA para niveles de TNFα.

Método de ELISA

Los niveles de TNFα se midieron usando ELISA en sándwich, Oliveira et al, Circ. SOC, 37, 301 - 306 (1992) cuya revelación se incorpora por referencia enteramente, usando un anti murino TNFα monoclonal de hámster (Genzime, Boston, MA) como en anticuerpo de captura y el policlonal de conejo antimurino TNFa (Genzime) como el anticuerpo secundario. Para la detección, el anticuerpo de cabras anticonejo conjugado con peroxidasa (Pierce, Rockford, IL) se adicionó, seguido por el sustrato para peroxidasa (1mg/ml de ortofenildiamina con peróxido de urea al 1%) . Los niveles de TNFα en las muestras de plasma de cada animal se calcularon de una curva estándar generada por TNFα recombinante murina (Genenzyme) .

Producción de citoquina estimulada por LPS en sangre total humana

Análisis: Las concentraciones del compuesto prueba se prepararon a concentraciones 10X y LPS preparada a 1µg/ml (concentración final de 50 ng/ml de LPS) y se adicionaron en volúmenes de 50 µl a tubos eppendorf de 1.5 mL. La sangre total humana heparinizada se obtuvo de voluntarios sanos y fue repartida en tubos eppendorf o placas multiceldas que contenían compuestos y LPS en volúmenes de 0.2 y 0.4 ml y los tubos incubados a 37 C. En algunos estudios, los compuestos se incubaron con sangre por hasta 30 min antes de la adición de LPS. Siguiendo una incubación de 4 horas, los tubos o placas se centrifugaron para remover las células y se retiró el plasma y sen congeló a - 80 C.

Medición de la citoquina: IL - beta y TNFalfa se cuantificaron usando ELISA estandarizada o tecnología similar. Las concentraciones de IL - 1beta o TNFalfa se determinaron a partir de curvas estandarizadas de la citoquina y valores IC50 para compuestos prueba (concentraciones que inhibieron 50% de producción de citoquina estimulada por LPS) se calcularon por análisis de regresión lineal.

Resultados

Los compuestos se considerarían activos si demostraran una IC50 de menos de 10 μM hasta una IC50 de menos de 0.0001 μM.

Los compuestos representativos de Fórmula (I) y (Ia) como se describe en los ejemplos 7 (c) , 8 (c) , 9, 10€, 11, 13, 14, 17, 18, 23 (c) y €, 24, 26, 28, 29 (c) , 53, 58, 69 - 72, 74, 76, 78, 91, 115, 118 (c) , 119, 121, 123, 124, 126, 127, 130, 131, 133, 136 - 140, 142, 144, 146, 163 (a) y (c) , 165 - 167, 169 - 176, 180 - 181, 184, 192, 205, 206, 211, 213 - 219, y 223, 224 se analizaron en el análisis anterior y se encontraron activos.

Los compuestos de los ejemplos 66 - 68, 73, 117, 128 - 129, 141, 143, 161, 162, 163 (b) y 226 demostraron una IC50 de más de 1.0 μM en éste análisis. El ejemplo 111 (c) en corridas múltiples proporcionaron un rango de datos, desde una IC50 de 0.040 μM a una IC50 de más de 0.1 μM en éste análisis. Mientras éstos compuestos se encontraron que inhibían más del 50% a 1μM de TNT - alfa, algunos de éstos compuestos se esperaría luego de analizarlos de nuevo con concentraciones en aumento que alcanzaran una inhibición del 50%.

Análisis de CSBP/p38 quinasa:

Este análisis mide la transferencia de CSBP/p38 catalizada de ^{32}P de ATP[a - ^{32}P] a un residuo de treonina en un péptido derivado (T669) en un factor receptor de crecimiento epidermal (EGFR) con la siguiente secuencia: KRELVEPL*T*GPSGAPNQALLR (residuos 661 - 681) . (Ver Gallager et al. "Regulation of stress induced cytokine production by pyridinyl imidazoles: inhibition of CSBP kinase" BioOrganic and medicinal chemistry, 1997, 5, 49 - 64) .

Las reacciones se llevaron a cabo en placas de 96 pozos de fondo redondeado (de Corning) en volúmenes de 3.0 ml. Las reacciones contenían (en concentración final) : 25mM Hepes, pH 7.5; 8mM $MgCl_2$; 0.17 mM ATP (la $Km_{[ATP]}$ de p38 (ver Lee et al, Nature 300, n72 pg. 639 - 746 (Dic. 1994)) ; 2.5 μCi de [g - 32ATP]; 0.2 mM ortovanadato de sodio; 1 mM DTT; 0.1% BSA; 10% glicerol, 0.67mM péptido T669 y 2 - 4 nM de p38 expresado en levaduras, activado y purificado. Las reacciones se iniciaron por la adición de [gama - 32P]Mg/ATP e incubados por 25 minutos a 37 C. Los inhibidores (disueltos en DMSO) se incubaron en una reacción mezcla sobre hielo por 30 minutos antes de adicionar el 32P ATP. La concentración de DMSO fue 0.16%. Las reacciones terminaron por adición de 10 μl de ácido fosfórico 0.3M y el péptido fosforilado se aisló de las reacciones capturándolo en filtros de fosfocelulosa p81. Los filtros se lavaron con ácidos fosfóricos 75 mM y se cuantificó el 32P utilizando un contador de destellos. Bajo esas condiciones, la actividad específica de p38 fue 400 - 450 pmol/pmol de enzima, y la actividad fue linear hasta por 2 horas de incubación. Los valores de actividad de quinasa se obtuvieron luego de restar los valores generados en ausencia de sustrato que fueron 10 - 15% de valores totales.

<u>Análisis de unión de quinasa por anisantropía de fluorescencia - Volumen estándar</u>

La enzima quinasa, ligando fluorescente y una concentración variable del compuesto prueba se incubaron juntos para alcanzar un equilibrio termodinámico bajo condiciones en las que en ausencia del compuesto prueba, el ligando fluorescente está significativamente (>50%) unido a la enzima en presencia de una concentración suficiente (>10x Ki) de un potente inhibidor la asintropía del ligando fluorescente sin unir es diferente por medición del valor unido.

La concentración de la enzima quinasa debe preferiblemente ser ≥2 x Kf. La concentración usada debe ser menor que la concentración de la enzima quinasa. La concentración usada debe ser menor que la

concentración de la enzima quinasa y preferiblemente menor de la mitad de la concentración de enzima quinasa.

El ligando fluorescente es el siguiente compuesto:

INSERT FIGURE

el cual es derivado de 5 - [2 - (4 - aminometilfenil - 5 - piridin - 4 - il - 1H - imidazol - 4 - il] - 2 - clorofenol y verde rodamina.

p38α humana recombinante fue expresada en proteina marcada con GST. Para activar ésta proteína, p38α 3.5 μM inactivada fue incubada en 50 mM de Tris - HCl pH 7.5, 0.1 mM EGTA, 0.1% mercaptoetanol, 0.1 mM vanadato de sodio, 10mM Mga., 0.1 mM ATP con 200nM MBP - MKK6 DD a 30 grados por 30 minutos. Siguiendo la activación p38α fue repurificada y la actividad evaluada usando un análisis estándar de unión al filtro.

Protocolo: Todos los componentes son disueltos en buffer de composición 62.5 mM HEPES, pH 7.5, 1.25 mM CHAPS, 1 mM DDT, 12.5 mM $MgCl_2$ con una concentración final de p38α de 12nM y 5 nM de ligando fluorescente. 30 μl de esta mezcla de reactivos se adiciona a los pozos que contienen 1 μl de varias concentraciones de compuestos pruebas (0.28 nM - 16.6 μM final) o un venículo de DMSO (3% final) en placas de micropruebas de 384 pozos NUNC y equilibradas por 30 - 60 minutos a temperatura ambiente. La anisotropía de fluorescencia fue leida en Molecular Device Aquest (excitación 485 nm/emisión 535 nm) .

Definiciones: Ki = constante de disociación para unión inhibitoria

Kf = constante de disociación par unión del ligando fluorescente

Análisis de volumen bajo de unión de quinasa por anisantropía de fluorescencia

La enzima quinasa, ligando fluorescente y concentración variable de compuesto prueba, son incubados juntos hasta alcanzar un equilibrio termodinámico bajo condiciones en las que en ausencia de compuesto prueba el ligando fluorescente está significativamente (>50%) unido a la enzima en la presencia de una concentración suficiente (>10 X Ki) de un inhibidor potente, la anisotropía del ligando fluorescente no unido es apreciablemente diferente del valor unido.

La concentración de la enzima quinasa debería ser preferiblemente 2 x Kf. La concentración de ligando fluorescente requerido dependerá en la instrumentación usada y a las propiedades fluorescentes y fisicoquímicas. La concentración usada debe ser menor de la concentración de la enzima quinasa, y preferiblemente menor de la mitad de la concentración de la enzima quinasa.

El ligando fluorescente es el siguiente compuesto:

INSERT FIGURE

que es derivado de 5 - [2 - (aminometilfenil -) - 5 - piridin - 4 - il - 1H - imidazol - 4 - il] - 2 - clorofenol y verde rodamina.

p38α humana recombinante fue expresada como una proteína marcada con GST. Para activar ésta proteína, 3.5 μM de p38α no activada fue incubada en 50 mM Tris - Hcl pH 7.5, 0.1 mM EGTA, 0.1% 2 -

mercaptoetanol, 0.1 mM de vanadato de sodio, 10 mM de Mga., 0.1 mM ATP con 200 nM MBP - MKK6 DD a 30 grados por 30 minutos. Siguiendo la activación, p38α fue repurificada y la actividad evaluada utilizando un análisis de unión al filtro.

Protocolo: Todos los componentes son disueltos en una composición de buffer de 62.5 mM HEPES, pH 7.5, 1.25 mM CHAPS, 1 mM DTT, 12.5 mM $MgCl_2$, con concentraciones finales de 12 nM de p38α y ligando fluorescente 5 nM. 30 µl de esta reacción mezcla se adiciona a celdas que contienen 0.1 µl de varias concentraciones de compuesto prueba (0.02 nM - 25 µM final) o vehículo DMSO (1.7% final) en microplacas de 384 pozos de volumen bajo Greiner y se equilibraron por 30 - 60 minutos a temperatura ambiente. La anisotropía de fluorescencia se lee en Molecular Devides Acquest (485 nm excitación, 535 nm de emisión) .

Definiciones: *Ki* = constante de disociación para el inhibidor de la unión

Kf = constante de disociación para unión del ligando fluorescente

Se nota que hay dos formatos de análisis mostrados anteriormente para el análisis de unión de quinasa por anisotropía de fluorescencia. La única diferencia entre estos dos análisis es el volumen utilizado y el tipo de placa. Se ha demostrado que no existe diferencia en potencia entre dos formatos, y que los análisis son considerados equivalentes. Los resultados descritos aquí pueden haber sido realizados por cualquiera de los dos formatos de análisis y no son diferenciados.

Resultados

Los compuestos son considerados activos en éste análisis si se demuestra una pIC50 mayor de 4.6 a aproximadamente una pIC50 de 9.0.

Los compuestos representativos de la fórmula (I) y (Ia) , como se describen en los ejemplos 1 (d) , 1 (g) , 2 (b) , 3 (b) , 4 (c) , 5, 6 (b) , 7 (c) , 7 (d) , 8 (c) , 10 (b) , (c) y (e) , 11 a 14, 15 (a) , (b) y (c) , 16 a 18, 19 (b) , 20, 21 (a) y (b) , 22, 23 (c) , (d) y (e) , 24 a 26, 27 (b) , 28, 29 (c) , 30 (c) , 31 (b) , 32, 33 (b) , 34 (d) , 35 a 37, 38 (b) , 39 a 55, 57 a 60, 62 a 83, 85, 86 (c) , 87 (b) , 88 (c) , 89 a 95, 96 (b) , 117, 118 (c) , 119 a 140, 142 a 148, 149 (a) y (c) 164 a 226 son activos en éste análisis.

Los compuestos de los ejemplos 19 (a) , 97, 98, 100 1 103, 104 (c) , 105 a 108, 110, 153, 160 demostraron una pIC50 aparente menor de 4.8 en éste análisis.

El compuesto del ejemplo 84 en corridas múltiples proporcionó un amplio rango de datos desde 5.3 a no menos de 5.75 de pIC50 en éste análisis. Los compuestos de los ejemplos 69, 141 y 161 proporcionaron un amplio rango de datos luego de múltiples corridas en un rango de 5.9 a menos de 4.8 de una pIC50 en éste análisis.

ANÁLISIS TR - FRET

Análisis estándar de transferencia de energía de resonancia por fluorescencia de quinasa resuelta con el tiempo

p38α recombinante humana fue expresada en una proteína marcada con His. Para activar esta proteína, 3 μM de p38α inactivada fue incubada en 200 mM Hepes 7.4, 625 mM de NaCl, 1 mM DDT con 27 nM de MKK6 activa (estado superior), 1mM ATP y 10 mM $MgCl_2$. La actividad de la p38α activada por MKK6 fue analizada utilizando análisis de transferencia de energía de resonancia por fluorescencia (TR - FRET).

GST - ATF2 biotinilada (residuos 19 - 96, 400 nM final), ATP (125M final) y $MgCl_2$ (5nM final) en buffer de ensayo (40 mM HEPES pH 7.4, 1 mM DDT) se adicionaron a los pozos que contenían 1 μl de varias concentraciones del compuesto o vehículo DMSO (3% final) en placas de 384 pozos negros NUNC. La reacción fue iniciada para la adición de p38 activada por MKK6 (100μM final) para dar un volumen total de 30 μl. Esta reacción fue incubada por 120 minutos a temperatura ambiente, luego terminadas por la adición de 15 μl de EDTA 100mM a pH 7.4. El agente de detección (15 μl) en buffer (100 mM HEPES pH 7.4, 150 mM NaCl, 0.1%, p/v BSA, 1mM DTT) que contenía anticuerpo policlonal antifosfotreonina ATF2 - 71 (Cell signaling technology, Beverly Massachussets, USA) marcada con europium quelado W - 1024 (Wallac OY, Turku, Finlandia), y estreptavidina marcada con APC (Prozyme, San Leandro, California, USA) fue adicionada y la reacción fue incubada por 60 minutos más a temperatura ambiente. El grado de fosforilación de GST - ATF2 se midió usando un lector de placas Packard Discovery (Perkin Elmer Life Sciences, Pangbourne, UK) como una proporción de transferencia de energía específica a 665 nm para referencia de la señal de europium a 620 nm.

<u>Análisis de transferencia de energía de resonancia por fluorescencia resuelta con el tiempo de volumen bajo</u>

p38α humana recombinate se expresó como una proteína marcada con His. Para activar ésta proteína, se incubó 3μM de p38α en Hepes 200 mM pH 7.4, 625 mM NaCl, 1 mM de DTT con MKK6 activa 27 nM (estado superior), 1 mM ATP y 10 mM $MgCl_2$. La actividad de la p38α activada por MKK6 fue analizada usando transferencia de energía de resonancia por fluorescencia resuelta con el tiempo (TR - FRET).

GST - ATF2 biotinilada (residuos 19 - 96, 400 nM final), ATP (125 μM final) y $MgCl_2$ (5 mM final) en buffer de análisis (40mM HEPES pH 7.4, 1 mM DTT) se adicionaron a pozos que contenían 0.1 μl de varias concentraciones de compuestos o vehículo de DMSO (1.7%) en placas de 384 pozos negros de poco volumen Greiner. La reacción fue iniciada por la adición de p38α activada por MKK6 (100 pM final) para dar un volumen total de 6 μl. La reacción se incubó por 120 minutos a temperatura ambiente, luego terminada por adición de 3 μl de reactivo de detección en buffer (100 mM HEPES pH 7.4, 150 mM NaCl, 0.1% p/v BSA, 1 mM DTT, 100 mM EDTA) que contenía anticuerpo policlonal antifosfotreonina - ATF2 - 71 (Cell signaling technology, Beverly Massachussets, USA) marcado con quelato europium W - 1024 (Wallac OY, Turku, Finlandia), y estreptavidina marcada con APC (Prozyme, San Leandro, California, USA). La reacción fue incubada por 60 minutos más a temperatura ambiente. El grado de fosforilación de GST - ATF2 fue medido usando un lector de placas BMG Rubystar (BMG, UK) como una proporción a 665 nm de transferencia de señal específica a la señal de referencia de europium a 620 nm.

Es de notar que hay dos formatos de ensayo que se mostraron anteriormente para el análisis de de energía de resonancia por fluorescencia resuelta con el tiempo para la transferencia de quinasa. La única diferencia entre estos dos ensayos es el volumen utilizado y el tipo de placa. Se ha demostrado que no hay diferencia en la potencia entre los dos formatos y a que los análisis son considerados como equivalentes. Los resultados descritos aquí pueden haberse realizando en cualquiera de los formatos y no se diferenciaron en cuanto a cual.

Resultados

Los compuestos se considerarían como activos en éste análisis si se demostrara una pIC50 mayor a 4.6 hasta una pIC50 mayor de 10.

Los compuestos representativos de la fórmula (I) y (Ia) como se describe en los ejemplos I (d) , 5, 7 (c) , 8c, 9, 11,13, 15 (c) , 16, 17, 19 (b) , 20, 21 (b) , 22, 24, 26,29 (c) , 30 (c) , 31 (b) , 32, 33 (b) , 34 (d) , 35 a 37, 38 (b) , 39 a 55, 58, 59, 62 a 85, 86 (c) , 87 (b) , 88 (c) , 89 a 95, 96 (b) , 98 a 101, 103, 106, 111 (c) , 112 a 116, 118 (c) , 119 a 140, 142 a 147, 149 (a) , 150 a 152, 156 (a) , (b) y (c) , 157 a 226, 227 (b) , 228 (b) , 229, 230 (b) se analizaron en el anterior análisis y se encontraron activos.

Los compuestos de los ejemplos 18 y 1 (g) luego de múltiples corridas proporcionaron un amplio rango de datos, desde 8.1 a menos de 4.8 de pIC50 en éste análisis. Los compuestos de los ejemplos 117, 108, 106, 104 (c) , 102, 97 luego de corridas múltiples proporcionaron un amplio rango de datos desde 6.8 hasta menos de 5.8 de pIC50 en éste análisis. Los compuestos de los ejemplos 105, 107 y 110 han demostrado una pIC50 de <5.8 en éste análisis. El compuesto del ejemplo 27 (b) demostró una pIC50 de < 4.8 en éste análisis.

Para propósitos de éste análisis HTRF y el análisis de anisostropía de fluorescencia de la unión de la quinasa:

pIC50	IC50	IC50 (μM)
4.00	100,000.0	100
5.00	100,000.0	10
6.00	1,000.0	1
7.00	100.0	0.1
8.00	10.0	0.01
9.00	1.0	0.001
10.00	0.1	0.0001

Producción de IL - 8 estimulado por TNF por neutrófilos humanos

Los efectos de los compuestos prueba en la producción de IL8 estimulada por TNF por nueutrófilos humanos se mide como sigue. Los neutrófilos son preparados a partir de sangre obtenida de donadores, usando métodos estándar. La sangre es recolectada en jeringas heparinizadas y colocadas sobre histopaque (30 ml/20ml) . Luego de la centrifugación el precipitado de glóbulos rojos es resuspendido en PBS y purificado en un gradiente de dextran. Los glóbulos rojos se lisan con agua por 40 seg, y los granulocitos se recolectan por centrifugación y se resuspenden a 1.5 x 10^6 células/ml. Las células son adicionadas (0.5 - 1 ml) a placas de 48 pozos que ya contenían el compuesto a una concentración final 1000X en DMSO solo o 10% de DMSO en RPMI1640 con 10% de FBS. TNF (concentración final 100 ng/ml) se usa como estímulo. Las células se incuban por aproximadamente 20 horas a 37°C, 5% de CO_2. Los niveles de IL - 8 en el sobrenadante libre de células son determinados por ELISA en sándwich, y se calcula la inhibición relativa a un control con DMPO pero no al control.

Resultados

Los compuestos se considerarían activos en este análisis si se demostrara una IC50 de menos de 10μM hasta un IC50 menor de 0.0001 μM, y fueron analizadas a concentraciones hasta de 100 nM.

Los compuestos representativos de Fórmula (I) y (Ia) como se describe en los ejemplos 2 (b) ,3 (b) , 7 (c) y (d) , 8 (c) , 9, 11 - 14, 15 (c) , 16 - 18, 19 (b) , 20, 21 (b) , 22, 23 (c) y €, 24, 26, 27 (b) , 28, 29 (c) , 30 (c) , 31 (b) , 32,33 (b) , 34 (d) , 35 - 37, 38 (b) , 38 - 48, 51 - 55, 58, 63 - 64, 70, 74 - 83, 85, 86 (c) , 87 (b) , 88 (c) , 89, 91 - 95, 111 (c) , 114, 117, 120 - 122, 124, 127, 130, 148, 151, 177 - 180, 182 - 189, 194, 196, 198, 200 - 201, 203 - 204, 227 (b) y 230 (a) se analizaron en el ensayo anterior y se encontraron que eran activos.

Los compuestos de los ejemplos 4 (c) 5, 6 (b) , 15 (b) , 23 (d) , 49 - 50, 62, 65, 84, 90, 96 (b) , 98 - 101, 103, 104 (c) , 105 - 110, 113, 116, 125, 146, 149 (c) , 152 - 155, 156 (a) , 156 (b) , 156 (c) , 159, 160, 197, 228 (b) , 229 y 230 (b) , demostraron una IC50 de más de 0.1 μM en éste análisis. Estos últimos compuestos fueron analizados a diferentes concentraciones superiores que el grupo de arriba. Mientras estos compuestos no se encontraron que inhibían la producción de IL - 8 a más del 50% a 100nM, algunos de estos serían esperados luego de reanalizarlos con concentraciones mayores hasta alcanzar 50% de inhibición.

Los compuestos de los ejemplos 71 y 72 demostraron una IC50 de más de 0.001 μM en este ensayo. Estos últimos compuestos se analizaron a diferentes concentraciones superiores que el grupo anterior.

Los compuestos de los ejemplos 1 (g) , 15 (a) , 19 (a) luego de múltiples corridas proporcionaron un amplio rango de datos desde una IC50 de 0.04 μM a una IC50 mayor de 0.1μM en éste análisis. El ejemplo 115 luego de múltiples corridas proporcionó un amplio rango de datos desde una IC50 de menos de 0.001 μM a más de 0.1μM en éste análisis. Mientras éstos compuestos no se encontraron que inhibían la producción de Il - 8 a más del 50% a 100nM, algunos de éstos se esperarían luego de reanalizarlos con mayores concentraciones que alcanzaran 50% de inhibición.

Modelo neutrofilia de LPS en ratas

El efecto de compuestos en el ingreso de neutrófilos a los pulmones en ratas desafiadas con LPS se evaluó como sigue. El compuesto prueba se suspende en una de las siguientes soluciones: 0.5% tween 80/PBS, 0.5% tween 80/ salina, 10% EtOh/salina (con pH ajustado a 2.0 u 8.0 con HCl o sin ajustar) , salina a pH 2.0, 6.5 u 8.0, 0.5% tragacanto, 1% DMSO/20% encapsin/salina, o tragacanto acidificado 5%. El proceso de suspensión puede ayudarse con el uso de un homogenizador de vidrio. Para administración intratraqueal, los animales son anestesiados con isoflurano inhalado y colocados en posición supina, la tráquea es entubada con una aguja de acero con sonda (1.5 pulgadas, número 22, bola pequeña) o un microasperor Penn - Century (Modelo IA - 1B) y 200 μl de solución dosis se administró. Los animales son visualmente monitoreados durante el proceso de recuperación, lo que típicamente ocurre dentro de dos minutos.

Las ratas tratadas con compuesto o vehículo (15 min - 24 horas de pretratamiento) fueron expuestas a un aerosol de LPS (100mg/kg i.p) y las vías aéreas se lavaron 5 veces con 5ml de fosfato buffer salino. Las células cosechadas se tiñeron (Diffquick) y cuantificaron para determinar datos totales y células diferenciales. En un estudio típico, los macrófagos representaron 40 - 70% de las células totales, y las células polimofonucleares 30 - 60% de las células totales. La inhibición de niveles de neutrófilo relativos a compuestos no control se calcula basándose en conteos diferenciales.

El análisis tiene condiciones variables, como concentración, tiempo de pretratamiento, forma del compuesto (cristalino, amorfo, sales, micronizados) y una aplicación húmeda o seca del compuesto.

Los datos son obtenidos como % de inhibición usando una concentración particular y tiempo de pretratamiento. Mientras el número de compuestos se encontró que era estadísticamente no significativo ($p>0.05$), se espera que luego de reanalizarlos con mayores concentraciones, y/o un cambio en el tiempo de pretratamiento, algunos de ellos pueden alcanzar significado estadístico ($p>0.05$).

Los compuestos representativos de éste invento han sido probados en éste análisis. Los compuestos de los ejemplos 8 (c), 11, 29©, 36, 40, 42, 70, 71, 72, 91, 92, 112, 118 (c), 119, 120, 127, 137, 138, 140, 144 y 200 se encontró que tenían inhibición significativa estadísticamente de los neutrófilos en al menos uno de los rangos de condiciones probados en este ensayo.

Los compuestos de los ejemplos 9, 17, 23 (e), 24, 28, 32, 34 (d), 37, 39, 53, 57, 60, 86 (c), 87 (b), 93, 124, 134, 148, 151, 166, 172, 176 y 179 se encontró que no tenían inhibición significativa estadísticamente de los neutrófilos en al menos uno de los rango de condiciones probadas en este ensayo.

Los compuestos de los ejemplos 7 (c), 23 (e), 26, 43, 60, 174 y 175 se encontró que eran inactivos en éste ensayo.

TNFα en análisis de daño cerebral traumático

Este análisis provee el examen de expresión de UNAM de factor de necrosis de tumor en regiones específicas del cerebro que siguen inducción experimental de daño cerebral traumático de fluido de percusión (TBI) en ratas. Ya que TNFα es capaz de inducir factor de crecimiento nervioso (NGF) y estimular la liberación de otras citoquinas de astrositos activados, esta alteración post - traumática en la expresión genética de TNFα juega un papel importante en tanto la respuesta aguda y regenerativa al trauma CNS. Un estudio adecuado puede encontrarse en WO97/35856 cuyo contenido es incorporado aquí por referencia.

Modelo de daño CNS para RNAm de IL - b

Este análisis caracteriza la expresión regional de RNAm de interleukina - 1B (IL - 1B) en regiones específicas del cerebro luego de daño traumático cerebral de percusión de fluido lateral (TBI) experimental en ratas. Los resultados de estos análisis indican que después de TBI, la expresión temporal del RNAm de IL - 1B es estimulado regionalmente en regiones específicas del cerebro. Estos cambios regionales en las citoquinas, como IL - 1B juegan un papel en las secuelas post traumáticas patológicas del daño cerebral. Un análisis adecuado puede encontrarse en WO 97/35856 cuya publicación es incorporada aquí por referencia.

Análisis de angiogénesis:

Descrito en WO97/32583, cuya publicación es incorporada aquí por referencia, es un análisis para determinación de angiogénesis inflamatoria que puede usarse para mostrar que la inhibición de citoquina para la destrucción de tejido de proliferación excesiva o inapropiada de los vasos sanguíneos.

Análisis de Rinoivirus/Influenza:

Las líneas celulares, rinovirus serotipo 39 y el virus de la influenza A/PR/8/34 se compraron de la ATCC. Las células BEAS - 2B se cultivaron de acuerdo a las instrucciones proporcionadas por ATCC usando BEGM (medio de crecimiento bronquio epitelial) obtenido de Clonetics Corp. Los cultivos celulares HELA, usados para detección y medición de virus, se mantuvieron en medio mínimo esencial de Tagle con 10% de suero fetal de ternero, 2 mM de l - glutamina y 10 mM de buffer HEPES (MEM).

Una modificación del método reportado por Subauste y colaboradores, *Supra*, para infección in vitro de células bronquioepiteliales humanas con rinovirus, fue utilizada en éstos estudios. Células BEAS - 2B (2 x 10^5/pozo) fueron cultivadas en pozos cubierto por colágeno por 24 horas antes de la infección con rinovirus. El rinovirus serotipo 39 se adicionó a los cultivos celulares por una hora de incubación a 34°C después del cual el inóculo fue reemplazado con medio fresco y los cultivos se incubaron por 72 horas adicionales a 34 °C.

Los sobrenadantes recolectados 72 horas post - infección se analizaron para concentración de proteína citoquina por ELISA usando kits disponibles comercialmente (R&D Systems). La cosecha de virus también fue determinada en sobrenadantes de cultivo usando un análisis de microtitulación en cultivos celulares HELA (*Sabauste et al, supra, 1995*). En cultivos tratados con inhibidores de quinasa p38, se adicionó la droga 30 minutos antes de la infección. Las existencias de los compuestos se prepararon en DMSO (10 mM de droga) y se almacenaron a - 20°C.

Para la detección de quinasa p38, los cultivos se incubaron en medio basal sin factores de crecimiento y aditivos para reducir los niveles endógenos de p38 quinasa activada. Las células se cosecharon a diferentes tiempos luego de la adición de rinovirus. La detección de quinasa p38 fosforilada en la tirosina por inmunoblot se analizó por un kit disponible comercialmente y fue llevada a cabo de acuerdo a las instrucciones del fabricante (PhosphoPlus p38 MAPK kit de anticuerpo: New England BioLabs Inc.).

En algunos experimentos, las células BEAS - 2B fueron infectadas con virus de la influenza (capa A/PR/8/34) en lugar del rinovirus. El sobredadante del cultivo fue recolectado 48 y 72 horas post - infección y analizados por ELISA para citoquina como se describe arriba.

Células y virus: Influenza A/PR/8/34 subtipo H1N1 (VR - 95 Colección de cultivos tipos americana, Rockville, MD) se cultivó en la cavidad alantóica de óvulos de gallina de 10 días. Siguiendo la incubación a 37°C, y refrigeración por 2 ½ horas a 4°C, el fluido alantóico fue recolectado, reunido y centrifugada (1,000 rcf; 15 min; 4°C) para remover las células. El sobrenadante fue alicuotado y almacenado a - 70°C. El título de el cultivo de virus de almacenamiento fue 1.0 X 10^{10} Dosis infectivas de cultivo de tejido/ml ($TCID_{50}$).

Procedimiento de inoculación: Ratones Balb/c hembras de 46 semanas de edad se obtuvieron de Charles River, Raleigh, NC. Los animales se infectaron intranasalmente. Los ratones se anestesiaron por inyección intraperitoneal de quetamina (40mg/kg; Fort Dodge Labs, Fort Dodge, Ia) y xilacina (5 mg/kg; Miles, Shawnee Misión, Ks) y luego inoculados con 100 TCID50 de PR8 diluida en PBS en 20 µl. Los animales se observaron diariamente para ver síntomas de infección. Todos los estudios animales se aprobaron pror SmithKline Beckham farmacéuticos comité institucional de cuidado y uso animal.

Titulación del virus: A varios tiempos post - infección, los animales se sacrificaron y los pulmones fueron asépticamente cosechados. Los tejidos se homogenizaron, en viales que contenían cuentas de vidrio de 1 micrón (Productos Biospec, Gartlesville, OK) y 1 ml de medio mínimo esencial de Eagle. Los restos celulares se clarificaron por centrifugación a 1,000 rcf por 15 minutos a 4°C, y los sobrenadantes fueron seriadamente diluidos en células de riñón canino Madin - Darby (MDCK). Luego de 5 días de incubación a 37°C (5% de CO_2), 50 µl de 0.5% de glóbulos rojos de pollo se adicionaron por pozo y se leyó aglutinación luego de 1 hora a temperatura ambiente. El título del virus se expresa como 50% de dosis infectiva de cultivo de tejido ($TCIF_{50}$) calculada por regresión logística.

ELISA: Los niveles de citoquina se midieron por ELISA cuantitativa usando kits disponibles comercialmente. Las muestras de oido se homogenizaron usando un moledor de tejido en PBS. Los restos celulares se clarificaron por centrifugación a 14,000 rpm por 5 minutos. Las concentraciones de citoquina y umbrales se determinaron como lo describe el fabricante; IL - 6, IFN - γ y KC (R&D Systems, Minneapolis, MN) .

Análisis de mieloperoxidasa: La actividad de mieloperoxidasa (MPO) fue determinada cinéticamente como se describe por Bradley y colaboradores (1982) . Brevemente, córnea de conejo fue homogenizada en Hexadecil trimetil - bromuro de amonio (HTAB) (Sigma Chemical Co. St. Louis, Mo.) que se disolvió en 0.5 m de buffer de fosfato de potasio (J.T. Baker Scientific, Phillipsburg, Nj) . Después de la homogenización, las muestras se sometieron a congelación - descongelación - sonicación (Cole - Palmer 8853, Cole Palmer, Vernon Hills, Il) 3 veces. Las suspensiones se clarificaron por centrifugación a 12,500 g por 15 minutos a 4 °C. La actividad enzimática MPO fue determinada por cambio colorimétrico en absorbancia durante una reacción de O - dihidrocloruro de dianisidina (ODI) 0.175 mg/ml (Sigma chemical co. St. Louis, Mo) . Las mediciones se llevaron a cabo usando un espectrofotómetro Beckman Du 640 (Fullerton, Ca.) ajustado con un mecanismo de control. 50µl de material a ser analizado se adicionó a 950 µl de ODI y se midió un cambio en absorbancia a una longitud de onda de 460 nm por 2 minutos a 25 °C.

Pletismografía de todo el cuerpo: Los ratones infectados con virus de la influenza se colocaron en una caja de pletismografía de todo el cuerpo con un volumen interno de aproximadamente 350 ml. Un flujo de are de un l/min se aplicó a la caja y los cambios en el flujo se midieron y registraron con Buxco XA adquisición de datos y sistema de análisis respiratorio (Buxco Electronics, Sharon, CT) . Se les permitió a los animales aclimatarse a la caja de pletismografía por 2 min antes de que los datos de flujo de registraran. Las mediciones de las vías aéreas se calcularon como Penh (pausa aumentada) . Se ha mostrado que Penh es un índice de obstrucción de las vías aéreas y se correlaciona con un incremento en presión intrapleural. El algoritmo para el cálculo de Penh es como sigue: Penh = [(tiempo expiratorio/tiempo de relajación) - 1]x (flujo pico expiratorio/flujo pico inspiratorio) donde el tiempo de relajación es la cantidad de tiempo requerido para 70% del volumen nidal en ser expirado.

Determinación de saturación de oxígeno arterial. Se usó un oxímetro de pulso manual 8500V con sensor lingual (Nonin medical Inc., Plymouth MN) se usó para determinar la saturación de oxígeno arterial diariamente $\%SpO_2$ como está descrito (SIDEC y colaboradores 1992, Agentes antimicrobioanos y quimioterapia 36:473 - 476) .

Los datos adicionales y modificaciones en el ensayo pueden encontrarse en PCT/US00/25386, (WO 01/19322) presentada el 15 de Septiembre de 2000, cuya publicación es incorporada aquí por referencia en su totalidad.

Todas las publicaciones, incluyendo pero no limitándose a las patentes y a las aplicaciones de patentes, citadas en esta especificación son incorporadas por referencia como si cada publicación individual fuera específicamente e individualmente indicada para ser incorporada por referencia aquí como un grupo total.

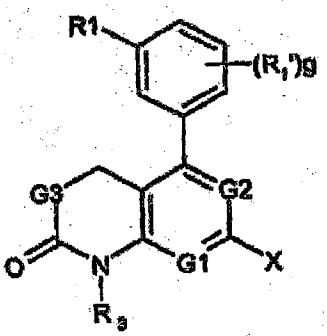
La descripción de arriba divulga totalmente el invento incluyendo la realización preferida. Las modificaciones y mejoras de la realización específicamente divulgadas aquí están dentro del alcance de las siguientes reivindicaciones. Sin más elaboración, se estima que aquel experto en el estado de la técnica usando la anterior descripción pueda usar el presente invento en su extensión total. Entonces, los ejemplos de aquí deben ser considerados solo como ilustrativos y no como una limitación del alcance del presente

invento de ninguna manera. Las realizaciones del invento en los cuales una propiedad exclusiva o privilegio es reivindicado se definen como sigue.

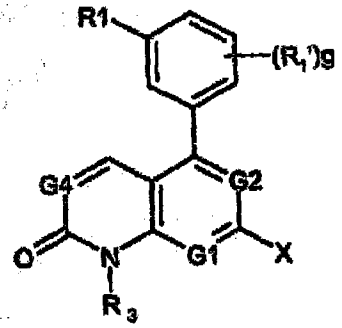
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Reivindicaciones:

1. Un compuesto de la formula:



(I)



(Ia)

en donde

G3 es NH;

G4 es nitrógeno;

R1 es C (Z) N (R10') (CR10R20) vRb, C (Z) O (CR10R20) vRb, N (R10') C (Z) (CR10R20) vRb; N (R10') C (Z) N (R10') (CR10R20) vRb; o N (R10'=OC (Z) (CR10R20) vRb;

R1' es independientemente seleccionado en cada ocurrencia a partir de halógeno, C1 - 4alquilo, C1 - 4alquilo halo - sustituido, ciano, nitro, (CR10R20) v'NRdRd', (CR10R20) v'C (O) R12, SR5, S (O) R5, S (O) 2R5, o (CR10R20) v'OR13;

Rb es hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 10 alquilo, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10 alquilo, heterocíclilo, o heterociclilC1 - 10 alquilo , tales fracciones excluyendo hidrógeno, pueden todas ser opcionalmente susituidas;

X es R2, OR2', S (O) mR2', (CH2) n'N (R10') S (O) mR2', (CH2) n'N (R10') C (O) R2', (CH2) n'NR4R14, (CH2) n'N (R2') (R2'') , o N (R10') - Rh - NH - C (=N - CN) NRqRq';

X1 es N (R11) , O, S (O) m, o CR10R20;

Rh es seleccionado de un C1 - 10alquilo opcionalmente sustituido, - CH2 - C (O) - CH2 - , - CH2 - CH2 - O - CH2 - CH2 - , - CH2 - C (O) N (R10') CH2 - CH2 - , - CH2 - N (R10') C (O) CH2 - , - CH2 - CH (OR10') - CH2, - CH2 - C (O) O - CH2 - CH2 - , o –CH2 - CH2 - O - C (O) CH2 - ;

Rq y Rq' son independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquiloC1 - 10alquilo, C5 - 7cicloalquenilo, C5 - 7cicloalquinilo - C1 - 10alquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde todas las fracciones, excluyendo hidrógeno, son opcionalmente sustituidas, o Rq y Rq' junto con el nitrógeno al cual

están fijadas formar un anillo opcionalmente sustituido de 5 a 7 miembros, tal anillo puede contener un heteroátomo adicional seleccionado de oxigeno, nitrógeno o azufre;

R2 es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

R2 es la fracción (CR10R20) q'X1 (CR10R20) qC (A1) (A2) (A3) , o (CR10R20) q'C (A1) (A2) (A3) ;

R2' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir;

R2'' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

en donde R2'' es la fracción (CR10R20) tX1 (CR10R20) qC (A1) (A2) (A3) ;

A1 es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A2 es es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A3 es hidrógeno o es C1 - 10 alquilo opcionalmente sustituido;

R3 esC1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquil C1 - 10 alquilo, arilo, arilC1 - 10 alquilo, heteroarilC1 - 10alquilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones se pueden opcionalmente sustituir;

R4 y R14 son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 4alquilo, arilo, arilC1 - 4 alquilo, heteroarilo, heterociclilo,C1 - 4 alquilo heterocíclico, heteroarilo o una fracción de heteroaril C1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o R4 y R14 junto con el nitrógeno al cual están unidos formar un anillo heterocíclico opcionalmente sustituido de 4 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de oxigeno, azufre o nitrógeno;

R4' y R14' son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno o C1 - 4 alquilo, o R4' y R14' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico de 5 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de NR9';

R5 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, c2 - 4 alquenilo, C2 - 4 alquinilo, o NR4'R14', excluyendo las fracciones SR5 siendo SNR4'R14', S (O) 2R5 siendo SO2H y S (O) R5 siendo SOH;

R9' es seleccionado independientemente en cada ocurrencia a partir de hidrógeno, o C1 - 4alquilo;

R10 y R20 son independientemente seleccionados en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R10' es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R11 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R12 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

R13 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

Rd y Rd' son cada uno independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, C3 - 6 cicloalquilo, C3 - 6 cicloalquilC1 - 4alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o Rd y Rd' junto con el nitrógeno al cual están unidas forman un anillo heterocíclico opcionalmente sustituido de 5 a 6 miembros, tal anillo opcionalmente puede contener un heteroátomo adicional seleccionado de oxigeno, azufre o NR9';

g es 0 o un entero con un valor de 1, 2, 3 o 4;

n' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 a 10;

m es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 0 2;

q es 0 o un entero con un valor de 1 a 10;

q' es 0, o un entero con un valor de 1 a 6;

t es un entero con un valor de 2 a 6;

v es 0 o un entero con un valor de 1 o 2;

v' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 o 2;

Z es independientemente seleccionado en cada ocurrencia de oxigeno o azufre; o una sal farmacéuticamente aceptable, solvato o derivado fisiológicamente funcional.

2. El compuesto según la reivindicación 1 el cual es la Formula (I) , o una sal farmacéuticamente aceptable, solvato o derivado fisiológicamente funcional del mismo.

3. El compuesto según la reivindicación 1 el cual es la Formula (Ia) , o una sal, solvato farmacéuticamente aceptables del mismo o derivado fisiológicamente funcional.

4. El compuesto según la reivindicación 1 en donde R1 es C (Z) N (R10') (CR10R20) vRb o N (R10') C (Z) (CR10R20) vRb.

5. El compuesto según la reivindicación 4 en donde R1 es C (Z) N (R10') (CR10R20) vRb.

6. El compuesto según la Reivindicación 1 en donde Rb es seleccionado de un alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, arilo opcionalmente sustituido, aril - C1 - 10 alquilo opcionalmente sustituido, o un C3 - 7 - cicloalquil - C1 - 10 alquilo opcionalmente sustituido.

7. El compuesto según la reivindicación 6 en donde Rb esa alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido, o un arilo opcionalmente sustituido.

8. El compuesto según la reivindicación 7 en donde Rb es propilo, isopropilo, tiazolilo, fenilo, o fenilo 4 - F.

9. El compuesto según la reivindicación 6 en donde Rb es un arilo opcionalmente sustituido o fracción aril - C1 - 10 alquilo, y el anillo de arilo sustituido independientemente en cada ocurrencia una o más veces por halógeno, alquilo, ciano, OR8, SR5; S (O) 2R5; C (O) Rj; C (O) ORj; - Z' - (CR10R20) s - Z' - , C1 - 10alquilo halo - sustituido ; o un arilo opcionalmente sustituido; y en donde

R8 es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 4alquilo, C1 - 4C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 4alquilo, arilo, arilC1 -

4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

Rj es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 4alquilo, arilo, aril - C1 - 4alquilo, heteroarilo, heteroaril - C1 - 4alquilo, heterociclilo, o una fracción C1 - 4alquilo heterocíclico, y en donde estas fracciones se pueden todas opcionalmente sustituir;

Z' es independientemente seleccionada en cada ocurrencia de oxigeno, o azufre;

s es un entero con un valor de 1, 2, o 3, independientemente seleccionado en cada ocurrencia.

10. El compuesto según la Reivindicación 1 o 9 en donde Rb es fenilo, o naftileno, 2 - fluorofenilo, 3 - fluorofenilo, 4 - fluorofenilo, 2,3 - difluorofenilo, 2,4 - difluorofenilo, 3,4 - difluorofenilo, 3,5 - difluorofenilo, 3 - clorofenilo, 4 - clorofenilo, 3 - cloro - 4 - fluorofenilo, 2 - metilfenilo, 3 - metilfenilo, 4 - metilfenilo, 6 - metilfenilo, 2 - metilfenilo, 3 - aminofenilo, 3,4 - dimetilfenilo, 4 - metil - 3 - fluorofenilo, 4 - trifluorofenilo, 4 - etoxifenilo, 4 - metoxifenilo, 3 - cianofenilo, 4 - cianofenilo, 4 - tiometilfenilo, 4 - acetilfenilo, 4 - dimetilaminofenilo, bencilo, fenetilo, fenilpropilo, 2,3 - difluoro - bencilo, 3,5 - difluoro - bencilo, bifenilo, 4' - feniloxifenilo, 4 - (1 - piperidinilsulfnil) - fenilo, o 3 - (aminocarbonil) fenilo.

11. El compuesto según la reivindicación 6 en donde Rb es un C1 - 10alquilo, o un C1 - 10 alquilo sustituido una o más veces, independientemente por halógeno, ciano, alcoxilo, tiol, o hidroxilo.

12. El compuesto según la reivindicación 11 en donde Rb es metilo, etilo, propilo, isopropilo, t - butilo, butilo, 1,2 - dimetilpropilo, 2,2 - dimetilpropilo, heptilo, 2 - metilpropilo, 2,2,2 - trifluoroetilo, 2 - fluoroetilo, cianometilo, cianoetilo, 2 - metoxi - etilo, 2 - hidroxipropilo, serinol, o etiltioetilo.

13. El compuesto según la reivindicación 6 en donde Rb es heteroarilo, heteroaril - C1 - 10 alquilo, heterociclilo o heterociclil - C1 - 10 alquilo opcionalmente sustituido.

14. El compuesto según la reivindicación 13 en donde Rb es un 1,3 - tiazol - 2 - ilo, 5 - metil - 1,3 - tiazol - 2 - ilo, isoquinolina, 3 - tiofeno, indolo - 5ilo, piridin - 3 - ilo, piridina - 4 - ilo, indazolilo, benzotiazolo, 2 - metil - 1,3 - benzotiazol - 5 - ilo, pirazol - 3 - ilo, 4 - morfolino, 2 - furanilo, 2 - furanilmetilo, 2 - tienilo, 2 - tienilmetilo, tetrahidro - 2H - piran - 4ilo, tetrahidro - 2H - piran - 4ilo - metilo, tetrahidro - 2 - furanilo, otetrahidro - 2 - furanilmetilo, 2,3 - dihidro - 1,4 - benzodioxin - 6 - ilo, 1H - imidazol - 4 - ilo o 1H - imidazol - 4 - il - etilo.

15. El compuesto según la reivindicación 1 en donde Rb es un C3 - 7 - cicloalquilo o c3 - 7 - cicloalquil - C1 - 10 alquilo.

16. El compuesto según la reivindicación 15 en donde Rb es ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, o ciclopentilmetilo.

17. El compuesto según la reivindicación 6 en donde Rb es seleccionado de Metil - 1,3 - benzotiazol - 5 - ilo, 4` - fluro - 3 - bifenilo, 4 - fluoro - fenilo, 2 - flurofenilo, 4 - clorofenilo, 3,5 - difluorofenilo, 3,4 - difluorofenilo, 2,4 - difluorofenilo, 4 - fluorofenotilo, 3 - clorofenilo, 3 - cloro - 4 - fluorofenilo, 4 - acetilfenilo, 4 - trifluorofenilo, 4 - metilo - 3 - fluoro - fenilo, 4 - tiometilfenilo, 4 - etiloxifenilo, 4 - metoxifrenilo, 3 - feniloxifenilo, 3 - metilfenilo, 2 - metilfenilo, 5 - metilo - 1,3 - tiazol - 2 - ilo, 3 - piridinilo, 4 - piridinilo, 4 - cianofenilo, 3 - cianofenilo, 4 - (fenilcarbonil) fenilo, 1H - indazol - 6 - ilo, o 3 - (aminosulfonil) fenilo.

18. El compuesto según la Reivindicación 1 en donde el r1' es independientemente seleccionado de halógeno, C1 - 4 alquilo, o c1 - 4 alquilo halo sustituido.

19. El compuesto según la reivindicación 18 en donde los sustituyentes son independientemente fluor, metilo, o CF3.

20. El compuesto según la reivindicación 18 o 19 en donde g es 1.

21. El compuesto según cualquiera de las reivindicaciones 1 a 3 en donde X es S (O) mR2.

22. El compuesto según cualquiera de las reivindicaciones 1 a 3 en donde X es (CH2) nNR4R14, o (CH2) nN (R2') (R2'').

23. El compuesto según la reivindicación 22 en donde X es (CH2) nNR4R14, y R4 y R14 son independientemente seleccionados de hidrógeno, C1 - 10 alquilo opcionalmente sustituido, arilo opcionalmente sustituido, aril - C1 - 4 alquilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, heterociclil - C1 - 4 alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroaril - C1 - 4 alquilo opcionalmente sustituido.

24. El compuesto según la reivindicación 23 en donde el C1 - 10 alquilo se puede sustituir una o mas veces, independientemente en cada ocurrencia con NR4'R14'; halógeno, hidroxilo, alcoxilo, (©NR4'R14'; o NR4'C (O) C1 - 10alquilo.

25. El compuesto según la reivindicación 24 en donde R4' y R14' son independientemente seleccionados de hidrógeno o un C1 - 4 alquilo.

26. El compuesto según la reivindicación 25 en donde X es 3 - (dietilamino) propilamino.

27. El compuesto según la Reivindicación 22 en donde X es (CH2) nNR4R14 y uno entre R4 y R14 es un heteroaril - C1 - 4 alquilo opcionalmente sustituido, y la fracción de heteroarilo es seleccionada de tienilo, pirrolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, imidazolilo, pirazolilo, triazolilo, piridazinilo, pirimidinilo, pirazinilo, benzoxazolilo, benzimidazolilo, y benzotiazolilo.

28. El compuesto según la reivindicación 27 en donde la fracción de heteroarilo es seleccionada de pirrolilo, oxazolilo, tiazolilo, imidazolilo, benzoxazolilo, benzimidazolilo, y benzotiazolilo.

29. El compuesto según la reivindicación 22 en donde X es (CH2) nNR4R14 y uno entre R4 y R14 es una fracción heterociclil - C1 - 4 alquilo seleccionada de tetrahidropirrola, tetrahidropirano, tetrahidrofurano, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo,g indolinilo, pirazolinilo, pirazolidinilo, piperidinilo, diazepinilo, piperazinilo, y morfolino.

30. El compuesto según la Reivindicación 29 en donde la fracción heterociclil - C1 - 4 alquilo es seleccionada de pirrolinilo, pirrolidinilo, piperidinilo, piperazinilo, y morfolino.

31. El compuesto según la reivindicación 22 en donde X es (CH2) nNR4R14 y R4 y R14 junto con el nitrógeno ciclizan para formar un anillo opcionalmente sustituido seleccionado de pirrolidina, piperidina, piperazina, y morfolina.

32. El compuesto según la Reivindicación 22 en donde el anillo R4 y R14 ciclizado es opcionalmente sustituido una o más veces independientemente por un alquilo opcionalmente sustituido, un arilo opcionalmente sustituido, un heteroarilo opcionalmente sustituido, un heterociclilo opcionalmente sustituido, (CR10R20) nN (R10') C (Z) OR7, o NR4'R14'.

33. El compuesto según la Reivindicación 32 en donde los sustituyentes opcionales son seleccionados de fenilo, pirrolidinilo, morfolino, piperazinilo, 4 - metil - 1 - piperazinilo, piperidinilo, 2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - ilo, 5 - cloro - 2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - ilo, difenilmetilo, metilo, etilo, propilo, butilo, amino, metilamino, y dimetilamino.

34. El compuesto según la Reivindicación 1 en donde X es R2 y R2 es un anillo heterocíclico o heterociclilalquilo opcionalmente sustituido una o más veces independientemente en cada ocurrencia por un heterociclilo opcionalmente sustituido, heterociclil - C1 - 10 alquilo, arilo, aril - C1 - 10 alquilo, C1 - 10 alquilo, (CR10R20) nNReRe', o (CR10R20) nN (R10') C (Z) OR7.

35. El compuesto según la Reivindicación 32 en donde R2 es seleccionado de 1,4` - bipiperin - 1 - ilo, 4 - metil - 1,4` - bipiperin - 1 - ilo, 4 - piperidinilamino, 4 - amino - 1 - piperidinilo, 2,2,6,6 - tetrametil - 4 - piperidinil) amino, 4 - metil - 1 - piperazinilo, (4 - morfolinil) - 1 - piperidinilo, (4 - metil - 1 - piperazinil) - 1 - piperidinilo, 4 - etil - 1 - piperazinilo, (2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - il) - 1 - piperidinilo, 5 - cloro - (2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - il) - 1 - piperidinilo, 4 - (1 - pirrolidinil) - 1 - piperidinilo, 4 - metilhexahidro - 1H - 1,4 - diazepin - 1 - ilo, 4 - propil - 1 - piperazinilo, o 4 - butil - 1 - piperazinilo.

36. El compuesto según la Reivindicación 35 en donde R2 es 1,4' - bipiperin - 1 - ilo, 4 - (1 - pirrolidinil) - 1 - piperdinilo, y 4 - metil - 1 - piperazinilo.

37. El compuesto según la Reivindicación 1 en donde R2 es opcionalmente sustituido una o más veces, independientemente en cada ocurrencia con C1 - 10alquilo, C1 - 10alquilo halo - sustituido, C2 - 10 alquenilo, C2 - 10 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 10alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 10alquilo, halógeno, - C (O) , ciano, nitro, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, heterociclilC1 - 10alquilo, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN, (CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR10 R20) nOC (Z) R6, (CR10 R20) nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR-10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7; y en donde n es independientemente seleccionado en cada ocurrencia a partir de 0 o un entero con un valor de 1 a 10;

R6 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 10 alquilo, C3 - 7 cicloalquilo, heterociclilo, heterociclil - C1 - 10 alquilo, arilo, aril - C1 - 10 alquilo, heteroarilo o heteroarilC1 - 10 alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno son opcionalmente sustituidas.

38. El compuesto según la reivindicación 38 en donde R2 es un alquilo opcionalmente sustituido.

39. El compuesto según la reivindicación 38 en donde el C1 - 10 alquilo es opcionalmente sustituido por (CR10 R20) nC (Z) R6, (CR10 R20) nOR6, o (CR10 R20) nNR4R14.

40. El compuesto según cualquiera de las Reivindicaciones 1 a 3 en donde R2 es (CR10R20) q'X1 (CR10R20) qC (A1) (A2) (A3) , o (CR10R20) q'C (A1) (A2) (A3) .

41. El compuesto según la reivindicación 40 en donde C1 es oxigeno o N (R10') .

42. El compuesto según la reivindicación 41 en donde al menos uno de A1, A2 o A3 es sustituido por (CR10R20) nOR6.

43. El compuesto según la Reivindicación 42 en donde q es 1 o 2, y q' es 0.

44. El compuesto según la Reivindicación 22 en donde X es (CH2) nN (R2') (R2'') , y R2' es un C1 - 10 opcionalmente sustituido, cicloalquilo, heterociclilo, heterociclil - C1 - 10 alquilo, heteroarilalquilo.

45. El compuesto según la reivindicación 1 o 44 en donde las fracciones R2', excluyendo hidrógeno son opcionalmente sustituidas 1 a 4 veces, independientemente en cada ocurrencia por C1 - 10alquilo, C1 - 10alquilo halo sustituido, C2 - 10 alquenilo, C2 - 10 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 10alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 10alquilo, halógeno, - C (O) , ciano, nitro, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, heterociclilC1 - 10alquilo, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN, (CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR10 R20) nOC (Z) R6, (CR10 R20) nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7; y en donde

R6 es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo; heterociclilo; heterociclilC1 - 10alquilo, arilo, arilC1 - 10alquilo, heteroarilo o

heteroarilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno son opcionalmente sustituidas;

R7 es independientemente seleccionado en cada ocurrencia de C1 - 6 alquilo, arilo, aril - C1 - 6 alquilo, heterociclilo, heterociclilC1 - 6alquilo, heteroarilo, o heteroarilC1 - 6alquilo, y en donde cada una de estas fracciones se pueden sustituir de manera opcional;

Re y Re' son cada uno independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C3 - 7cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo; arilo, aril - C1 - 4alquilo, heterociclilo, C1 - 4alquilo heterocíclico, heteroarilo o un heteroarilC1 - 4alquilo; o Re y Re' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico opcionalmente sustituido de 4 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de oxigeno, azufre o nitrógeno; y

en donde cada una de estas fracciones, excluyendo hidrógeno, se puede sustituir 1 a 4 veces, independientemente en cada ocurrencia por halógeno; hidróxilo; C1 - 10alquilo hidroxilo sustituido; C1 - 10alcoxilo; C1 - 10alcoxilo halo sustituido; amino, C1 - 4alquilamino mono - & di - sustituido; S (O) mRf; C (O) Rj; C (O) ORj; (CR10R20) nN (R10') C (Z) OR7; (CR10R20) nN (R10') C (Z) NRdRd'; C (O) NR4'R14'; NR4'C (O) C1 - 10alquilo; NR4'C (O) arilo; ciano; nitro, C1 - 10alquilo; C3 - 7cicloalquilo; C3 - 7cicloalquilC1 - 10alquilo; C1 - 10alquilo halo sustituido; arilo, arilC1 - 4alquilo, heterociclilo, C1 - 4alquilo heterocíclico, heteroarilo, o heteroC1 - 4alquilo, y en donde estos arilo, heterociclilo, y heteroarilo que contienen fracciones se pueden sustituir opcionalmente una o dos veces independientemente en cada ocurrencia por halógeno, C1 - 4alquilo, hidroxilo,g C1 - 4alquilo hidroxilo - sustituido, C1 - 10alcoxilo, S (O) malquilo, amino, C1 - 4alquilamino mono - &di - sustituido, C1 - 4alquilo, o CF3;

Rf es independientemente seleccionado en cada ocurrencia de C1 - 10alquilo, arilo, aril - C1 - 10alquilo, heteroarilo, heteroaril - C1 - 10alquilo, heterociclilo, o una fracción C1 - 10alquilo heterocíclico, y en donde estas fracciones se pueden todas opcionalmente sustituir;

R4' y R14' son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno o C1 - 4 alquilo, o R4' y R14' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico de 5 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de NR9';

Rj es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 4alquilo, arilo, aril - C1 - 4alquilo, heteroarilo, heteroaril - C1 - 4alquilo, heterociclilo, o una fracción C1 - 4alquilo heterocíclico, y en donde estas fracciones excluyendo hidrógeno se pueden todas opcionalmente sustituir; y

n es 0 o un entero con un valor de 1 a 10, y es independientemente seleccionado en cada ocurrencia.

46. El compuesto según la Reivindicación 45 en donde R2' es un anillo heterocíclico o alquilo heterocíclico sustituido una o más veces, independientemente por C1 - 10 alquilo, arilo, arilalquilo, (CR10R20) nNReRe', o (CR10R20) nN (R10') C (Z) OR7.

47. El compuesto según la reivindicación 22 en donde la fracción (CH2) nN (R2') (R2'') es 1 - (fenilmetil) - 4 - piperidinamina, 2 - [4 - (fenilmetil) - 1 - piperazinil]etilamina, 2 - (1 - piperidinil) etilamina, 2 - (1 - metil - 2 - pirrolidin) etilamina, 2 - (1 - metil - 2 - pirrolidin) etilamina, 1 - [(fenilmetil) - 3 - pirrolidin]amina, 3 - [(1 - pirrolidin) propil]amina, 3 - [(hexahidro - 1H - azepin - 1 - il) propil]amina, (1 - metil - 4 - piperidinil) amina, 2 - [(4 - morfolinil) etil]amina, 2 - [(1 - pirrolidinil) etil] - amina, o [(1 - etil - 2 - pirrolidinil) metil]amina.

48. El compuesto según la Reivindicación 45 en donde R2' es un C1 - 10alquilo sustituido por (CR10R20) nNR3Re' o (CR10R20) nNReRe'C1 - 4alquilNReRe'.

49. El compuesto según la Reivindicación 48 en donde Re y Re' son independientemente seleccionados a partir de metilo, etilo, isopropilo, n - butilo, o t - butilo, y n=0.

50. El compuesto según la reivindicación 1, 22 o 44 en donde (CH2) nN (R2') (R2'') es 3 - (dimetilamino) propil (metil) amina, 3 - (dietilamino) propilamina, propilamina, (2,2 - dimetilpropil) amina, (2 - hidroxipropil) amino, 2 - (dimetilamino) etilamina, 2 - (dimetilamino) etil (metil) amina, 3 - (dimetilamino) propilamina, 2 - (metilamino) etilamino, [(1 - metiletil) amino]etilamina, 3 - (dietilamino) propilamina, 3 - (dibutilamino) propilamina, 3[(1 - metiletil) amino]propilamina, 3 - (1,1 - dimetiletil) aminopropilamina, 3 - (dimetilamino) - 2,2 - dimetilpropilamina, 4 - (dietilamino) - 1 - metilbutilamina, o 3 - [[3 - (dimetilamino) propil] - (metil) amina.

51. El compuesto según cualquiera de las reivindicaciones 1 a 3 en donde R3 es un c1 - 10 alquilo opcionalmente sustituido, c3 - 7 - cicloalquilo, c3 - 7 - cicloalquilalquilo, o arilo.

52. El compuesto según la Reivindicación 51 en donde R3 es sustituido una o mas veces, independientemente en cada ocurrencia, con halógeno, - C (O) , ciano, nitro, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, heterociclilC1 - 10alquilo, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN, (CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR10 R20) nOC (Z) R6, (CR10 R20) nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7; y en donde

R6 es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo; heterociclilo; heterociclilC1 - 10alquilo, arilo, arilC1 - 10alquilo, heteroarilo o

heteroarilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno son opcionalmente sustituidas;

R7 es independientemente seleccionado en cada ocurrencia de C1 - 6 alquilo, arilo, aril - C1 - 6 alquilo, heterociclilo, heterociclilC1 - 6alquilo, heteroarilo, o heteroarilC1 - 6alquilo, y en donde cada una de estas fracciones se pueden sustituir de manera opcional;

n es 0 o un entero con un valor de 1 a 10, y es independientemente seleccionado en cada ocurrencia.

53. El compuesto según la reivindicación 52 en donde el R3 es un arilo opcionalmente sustituido.

54. El compuesto según la reivindicación 53 en donde el arilo es un fenil sustituido una o más veces independientemente en cada ocurrencia por halógeno, (CR10R20) nOR6, C1 - 10 alquilo, (CR10R20) nNR16R26, o alquilo halo - sustituido.

55. El compuesto según la Reivindicación 54 en donde el fenilo es sustituido una o más veces independientemente por halógeno, hidroxilo, alcoxilo, amino, alquilo, o CF3.

56. El compuesto según la reivindicación 55 en donde el fenilo es di - sustituido independientemente en cada ocurrencia por halógeno o metilo.

57. El compuesto según la reivindicación 56 en donde R3 es 2,6 - difluorofenilo.

58. El compuesto según la reivindicación 1 en donde R3 es 2,6 - difluoro - fenilo, R1' es independientemente seleccionado en cada ocurrencia de hidrógeno, fluor, o metilo; g es 1 o 2; R1 es C (Z) N (R10') (CR10R20) vRb, Rb es C1 - 10 alquilo o un arilo opcionalmente sustituido; X es (CH2) nN (R2') (R2''), n es 0, y R2' es un alquilo sustituido por (CR10R20) nNReRe'.

59. El compuesto según la reivindicación 58 en donde el compuesto es de la Formula (Ic), Re y Re' son independientemente seleccioanados de metilo, etilo, isopropilo, n - butilo, o t - butilo, Rb es C1 - 10alquilo, g es 1; C (Z) N (R10R20) vRb, y Z es oxigeno, R10' es hidrógeno, y v=0.

60. El compuesto según la Reivindicación, el cual es:

{1 - [4 - {5 - [(Ciclobutilamino) carbonil] - 2 - metilfenil} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - piperidinil}carbamato de 1,1 - dimetiletilo;

3 - [2 - (4 - Amino - 1 - piperadinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - *N* - ciclobutil - 4 - metilbenzamida;

{1 - [4 - (5 - {[(Ciclopropilmetil) amino]carbonil} - 2 - metilfenil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - piperidinil}carbamato de 1,1 - dimetiletilo;

3 - [2 - (4 - Amino - 1 - piperadinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - *N* - (ciclopropilmetil) - 4 - metilbenzamida;

3 - [2 - (4 - Amino - 1 - piperadinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - *N* - [2 - (4 - fluorofenil) etil] - 4 - metilbenzamida;

(1 - {8 - (2,6 - difluorofenil) - 4 - [5 - ({[2 - (4 - fluorofenil) etil]amino}carbonil) - 2 - metilfenil] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il} - 4 - piperidinil) carbamato de 1,1 - dimetiletilo;

3 - [2 - [(2 - Aminoetil) (metil) amino] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - *N* - (ciclopropilmetilo) - 4 - metilbenzamida;

N - (Ciclopropilmetil) - 3 - (8 - (2,6 - difluorofenil) {[2 - (metilamino) etil]amino} - - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il];

N - (Ciclopropilmetil) - 3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (4 - piperidinilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - metilbenzamida;

4 - {[4 - (5 - {[(Ciclopropilmetil) amino]carbonil} - 2 - metilfenil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il]amino} - 1 - piperidinecarboxilato de 1,1 - dimetiletilo;

N - (3 - {8 - (2,6 - Difluorofenil) - 7 - oxo - 2 - [(2,2,6,6 - tetrametil - 4 - piperidinil) amino] - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metilfenil) - 3 - tiofenecarboxamida;

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dietilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il) - N - (4 - fluorofenil) - 4 - metilbenzamida;

3 - {8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) - propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiloxi) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenecarboxamida;

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N - {3 - [2 - (4 - amino - 1 - piperadinil) - 8 - (2,6 - difluorofenil) - 2 - (dimetilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il] - 4 - metilfenil} - 3 - tiofenecarboxinamida;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (dimetilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenecarboxinamina;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (etiloxi) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenecarboxinamina;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenecarboxinamina;

3 - [2 - (4 - Amino - 1 - piperadinil) - 8 - (2,6 - difluorofenil) - 2 - (dimetilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - (fenilmetil) benzamida;

3 - {8 - (2,6 - Difluorofenil) - 7 - oxo - 2 - [(2,2,6,6 - tetrametil - 4 - piperidinilamino] - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

3 - {8 - (2,6 - Difluorofenil) - 2 - [[3 (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

3 - (8 - (2,6 - Difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

3 - (8 - (2,6 - Difluorofenil) - 2 - {[2 - (metillamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

(2 - {[8 - (2,6 - difluorofenil) - 4 - (2 - metil - 5 - {[(fenilmetil) amino]carbonil}fenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il]amino}etil) metilcarbamato de 1,1 - dimetiletilo;

3 - [8 - (2,6 - Difluorofenil) - 2 - ({2 - [(1 - metiletil) amino]etil}amino) - 7 - oxo - 2 - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

3 - [8 - (2,6 - Difluorofenil) - 7 - oxo - 2 - (4 - piperidinilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - (fenilmetil) benzamida;

4 - {[8 - (2,6 - Difluorofenil) - 4 - (2 - metil - 5 - {[(fenilmetil) amino]carbonil}fenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il]amino} - 1 - piperidinecarboxilato de 1,1 - dimetiletilo;

3 - {8 - (2,6 - Difluorofenil) - 2 - [(1 - metil - 4 - piperidinil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metil - *N* - (fenilmetil) benzamida;

N - (3 - {8 - (2,6 - difluorofenil) - 7 - oxo - 2 - [(2,2,6,6 - tetrametil - 4 - piperidinil) amino] - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metilfenil) - 3 - fluoro - 4 - metilbenzamida;

N - {3 - [2 - (4 - amino - 1 - piperidinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida;

N - {3 - {8 - (2,6 - difluorofenil) - 2 - (etiloxi) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida;

N - (3 - {8 - (2,6 - difluorofenil) - 2 - [(1 - metiletil) oxi] - 7 - oxo - 2 - [(2,2,6,6 - tetrametil - 4 - piperidinil) amino] - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il} - 4 - metilfenil) - 3 - fluoro - 4 - metilbenzamida;

N - {3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (4 - piperidinilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida;

4 - {[8 - (2,6 - difluorofenil) - 4 - (5 - {[(3 - fluoro - 4 - metilfenil) carbonil]amino} - 2 - metilfenil) - 7 - oxo - tetrahidropirimido[4,5 - *d*]pirimidin - 2 - il]amino} - 1 - piperidinecarboxilato de 1,1 - dimetiletilo;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (dimetilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbnzamida;

3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - *d*]pirimidin - 4 - il] - 4 - metil - *N* - propilbenzamida; o

61. El compuesto según la reivindicación 1 el cual es:

N - (Ciclopropilmetil) - 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilbenzamida

N - (Ciclopropilmetil) - 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilbenzamida;

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenocarboxamida;

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenocarboxamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfinil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenocarboxamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (fenilmetil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - 4 - metil - N - (fenilmetil) benzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - propilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - propilbenzamida; o

Una sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable del mismo.

62. Un compuesto según la reivindicación 1 la cual es

N - {3 - [2 - (4 - amino - 1 - piperidinil) - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (etiloxi) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - (3 - [8 - (2,6 - difluorofenil) - 2 - [(1 - metiletil) oxi] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 7 - oxo - 2 - (4 - piperidinilamino) - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (dimetilamino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - N - propilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - metiletil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (metilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [[2 - (dimetilamino) etil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [4 - (metilamino) - 1 - piperidinil] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [[3 - (dimetilamino) propil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - 4 - metil - N - (1 - metiletil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - ({2 - [(1 - metiletil) amino]etil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [[2 - (dimetilamino) etil] (metil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - 4 - metil - N - (1 - metiletil) benzamida

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

3 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (metilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [(1 - metil - 4 - piperidinil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (dimetilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 4 - metil - N - (1 - metiletil) benzamida

3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

3 - (8 - (2,6 - difluorofenil) - 2 - {[3 - (dimetilamino) propil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [2 - {[3 - (dietilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - {8 - (2,6 - difluorofenil) - 2 - [(1H - imidazol - 2 - ilmetil) amino] - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il} - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [2 - {[3 - (dibutilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1 - metiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - {8 - (2,6 - difluorofenil) - 2 - ({3 - [(1,1 - dimetiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [2 - {[3 - (dibutilamino) propil]amino} - 8 - (2,6 - difluorofenil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1 - metiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil –N - (1 - metiletil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - ({3 - [(1,1 - dimetiletil) amino]propil}amino) - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il] - 4 - metil –N - (1 - metiletil) benzamida

Una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable.

63. Un compuesto la fórmula general (I) o (Ia) según la reivindicación 1, como se describió en cualquiera de los ejemplos 1 a 230 en la presente, o un tautómero, diastereómero, enantiomero, o sl del mismo.

64. Un compuesto como se define en cualquiera de los ejemplos 1 a 230 o una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable.

65. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable según la reivindicación 1 y un vehículo o diluyente farmacéuticamente aceptable.

66. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, o una sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable según la reivindicación 1, en mezcla con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables, para administración de manera intravenosa, intramuscular, subcutanea, intranasal, inhalación oral, intrarectal, intravaginal o intraperitoneal.

67. Un método para tratar un componente inflamatorio de una enfermedad mediada por CSBP/RK/p38 el mamífero en necesidad del mismo, tal método comprende administración a dicho mamífero de una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable, según la reivindicación 1.

68. El método según la reivindicación 67 en donde la enfermedad mediada por CSBP/RK/p38 es artritis soriática, síndrome de Reiter, gota, artritis traumática, artritis rubeola, sinovitis aguda, artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa, y otra condición artrítica, sepsis, choque séptico, choque endotóxico, sepsis gram negativa, síndrome de choque tóxico, malaria cerebral, meningitis, ataque isquémico y hemorrágico, neurotrauma/lesión de cabeza cerrada, asma, síndrome de distrés respiratorio en el adulto, enfermedad inflamatoria pulmonar

crónica, enfermedad pulmonar obstructiva crónica (COPD) , silicosis, sarcososis pulmonar, enfermedad de resorción ósea, osteoporosis, restenosis, lesión por reperfusión cardiaca y cerebral y renal, falla cardiaca congestiva, cirugía de bypass arterial coronario (CABG) , trombosis, glomerulonefritis, falla renal crónica, diabetes, retinopatia diabética, degeneración macular, aterosclerosis, retinopatía diabética, degeneración macular, crecimiento tumoral y metástasis, enfermedad angiogénica, neumonía inducida por influencia, eczema, dermatitis de contacto, soriasis, quemadura solar, o conjuntivitis.

69. Un método para tratar la inflamación asociada con resfriado común o una infección viral respiratoria causada por rinovirus humano (HRV) , otros enterovirus, coronavirus, virus de la influenza, virus de la parainfluenza, virus sincitial respiratorio, o adenovirus en un humano en necesidad del mismo tal método comprende administración a dicho, no una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable según la reivindicación 1.

70. El método según la Reivindicación 69 en donde la infección viral respiratoria exacerba el asma, bronquitis crónica, enfermedad pulmonar obstructiva crónica, otitis media, sinusitis, o en donde la infección viral respiratoria está asociada con una infección bacteriana secundaria, otitis media, sinusitis, o neumonía.

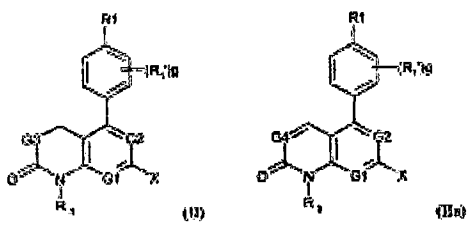
71. Un método para tratar inflamación en un mamífero en necesidad del mismo que comprende administración a dicho mamífero de una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 62.

72. Un método para tratar artritis traumática, artritis rubeola, sinoviitis aguda, artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa y otra condición artrítica, en un mamífero en necesidad del mismo, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 62.

73. Un método para tratar asma, síndrome de distrés respiratorio adulto, enfermedad inflamatoria pulmonar, o enfermedad pulmonar obstructiva crónica (COPD) en un mamífero en necesidad del mismo, que comprende administrar a dicho mamífero una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 62.

74. Un método para tratar aterosclerosis, enfermedad intestinal inflamatoria, enfermedad de Crohn, o colitis ulcerativa, en un mamífero en necesidad del mismo, comprendiendo administración a dicho mamífero de una cantidad efectiva de un compuesto según cualquiera de las reivindicaciones 1 a 62.

75. Un compuesto de la formula :



en donde

G1, y G2 son independientemente nitrógeno;

G3 es NH;

G4 es nitrógeno;

R1 es C (Z) N (R10') (CR10R20) vRb, C (Z) O (CR10R20) vRb, N (R10') C (Z) (CR10R20) vRb; N (R10') C (Z) N (R10') (CR10R20) vRb; o N (R10'=OC (Z) (CR10R20) vRb;

R1' es independientemente seleccionado en cada ocurrencia a partir de halógeno, C1 - 4alquilo, C1 - 4alquilo halo - sustituido, ciano, nitro, (CR10R20) v'NRdRd', (CR10R20) v'C (O) R12, SR5, S (O) R5, S (O) 2R5, o (CR10R20) v'OR13;

Rb es hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 10 alquilo, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10 alquilo, heterocíclilo, o heterociclilC1 - 10 alquilo , tales fracciones excluyendo hidrógeno, pueden todas ser opcionalmente susituidas;

X es R2, OR2', S (O) mR2', (CH2) n'N (R10') S (O) mR2', (CH2) n'N (R10') C (O) R2', (CH2) n'NR4R14, (CH2) n'N (R2') (R2'') , o N (R10') - Rh - NH - C (=N - CN) NRqRq';

X1 es N (R11) , O, S (O) m, o CR10R20;

Rh es seleccionado de un C1 - 10alquilo opcionalmente sustituido, - CH2 - C (O) - CH2 - , - CH2 - CH2 - O - CH2 - CH2 - , - CH2 - C (O) N (R10') CH2 - CH2 - , - CH2 - N (R10') C (O) CH2 - , - CH2 - CH (OR10') - CH2, - CH2 - C (O) O - CH2 - CH2 - , o –CH2 - CH2 - O - C (O) CH2 - ;

Rq y Rq' son independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquiloC1 - 10alquilo, C5 - 7cicloalquenilo, C5 - 7cicloalquinilo - C1 - 10alquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde todas las fracciones, excluyendo hidrógeno, son opcionalmente sustituidas, o Rq y Rq' junto con el nitrógeno al cual están fijadas formar un anillo opcionalmente sustituido de 5 a 7 miembros, tal anillo puede contener un heteroátomo adicional seleccionado de oxigeno, nitrógeno o azufre;

R2 es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

R2 es la fracción (CR10R20) q'X1 (CR10R20) qC (A1) (A2) (A3) , o (CR10R20) q'C (A1) (A2) (A3) ;

R2' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir;

R2'' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

en donde R2'' es la fracción (CR10R20) tX1 (CR10R20) qC (A1) (A2) (A3);

A1 es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A2 es es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A3 es hidrógeno o es C1 - 10 alquilo opcionalmente sustituido;

R3 esC1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquil C1 - 10 alquilo, arilo, arilC1 - 10 alquilo, heteroarilC1 - 10alquilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones se pueden opcionalmente sustituir;

R4 y R14 son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 4alquilo, arilo, arilC1 - 4 alquilo, heteroarilo, heterociclilo,C1 - 4 alquilo heterocíclico, heteroarilo o una fracción de heteroaril C1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o R4 y R14 junto con el nitrógeno al cual están unidos formar un anillo heterocíclico opcionalmente sustituido de 4 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de oxigeno, azufre o nitrógeno;

R4' y R14' son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno o C1 - 4 alquilo, o R4' y R14' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico de 5 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de NR9';

R5 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, c2 - 4 alquenilo, C2 - 4 alquinilo, o NR4'R14', excluyendo las fracciones SR5 siendo SNR4'R14', S (O) 2R5 siendo SO2H y S (O) R5 siendo SOH;

R9' es seleccionado independientemente en cada ocurrencia a partir de hidrógeno, o C1 - 4alquilo;

R10 y R20 son independientemente seleccionados en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R10' es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R11 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R12 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 -

7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

R13 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

Rd y Rd' son cada uno independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, C3 - 6 cicloalquilo, C3 - 6 cicloalquilC1 - 4alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o Rd y Rd' junto con el nitrógeno al cual están unidas forman un anillo heterocíclico opcionalmente sustituido de 5 a 6 miembros, tal anillo opcionalmente puede contener un heteroátomo adicional seleccionado de oxigeno, azufre o NR9';

g es 0 o un entero con un valor de 1, 2, 3 o 4;

n' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 a 10;

m es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 0 2;

q es 0 o un entero con un valor de 1 a 10;

q' es 0, o un entero con un valor de 1 a 6;

t es un entero con un valor de 2 a 6;

v es 0 o un entero con un valor de 1 o 2;

v' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 o 2;

Z es independientemente seleccionado en cada ocurrencia de oxigeno o azufre; o una sal farmacéuticamente aceptable, solvato o derivado fisiológicamente funcional.

76. Un compuesto según la reivindicación 75 en donde:
4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 1,3 - tiazol - 2 - ilbenzamida

ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzoico

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 1,3 - tiazol - 2 - benzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - propilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - fenilbenzamida.

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) benzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N,N - dimetilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - metilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) benzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 3 - metil - N - (1 - metiletil) benzamida

ácido 4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 3 - metilbenzoico

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 3 - metil - N - propilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimeyilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 3 - metil - fenililbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - (4 - fluorofenil) - 3 - metilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - N ,3 - trimetilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - N - 3 - dimetilbenzamida

4 - (8 - (2,6 - difluorofenil) - 2 - {[2 - (dimetilamino) etil]amino} - 7 - oxo - 5,6,7,8 - tetrahidropirimido[4,5 - d]pirimidin - 4 - il) - 3 - metilbenzamida, o una sal, solvato o derivado fisiológicamente funcional del mismo, farmacéuticamente aceptable.

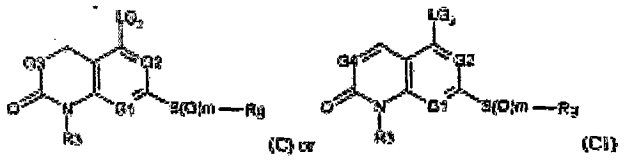
77. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, o sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable según la reivindicación 75, en mezcla con uno o más vehículos diluyentes o excipientes farmacéuticamente aceptables.

78. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, o sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable según la

reivindicación 75 en mezcla con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables, para administración por vía intravenosa, intramuscular, subcutánea, intranasal, inhalación oral, intrarectal, intravaginal o intraperitoneal.

79. Un método para tratar un componente inflamatorio de una enfermedad mediada por CSBP/RK/p38 quinasa en un mamífero en necesidad del mismo, tal método comprende administración a dicho mamífero de una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable, según la reivindicación 75.

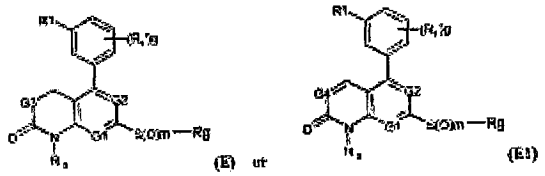
80. Un compuesto de la formula:



(C) or (CI)

en donde,
G1, y G2 son independientemente nitrógeno;
LG2 es cloro, bromo, yodo, o O - S (O) 2CF3;
R3 es C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquil C1 - 10 alquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones se pueden opcionalmente sustituir.

81. Un compuesto de la formula:



(E) or (EI)

en donde,
G1, G2, G3 y G4 son como se describieron para la Formula (I) en la presente;
m es 0 o un entero con un valor de 1 o 2;
Rg es un C1 - 10alquilo;
LG2 es cloro, bromo, yodo, o O - S (O) 2CF3;
R3 es C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquil C1 - 10 alquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones se pueden opcionalmente sustituir.

82. El compuesto según la reivindicación 81 en donde R3 es un 2,6 - difluorofenilo, y Rg es metilo.

83. El compuesto según la reivindicación 81 el cual es

ácido 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - metilbenzoico

N - (Ciclopropilmetil) - 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilbenzamida

N - (Ciclopropilmetil) - 3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - (4 - fluorofenil) - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenocarboxamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - tiofenocarboxamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - 4 - metil - N - (fenilmetil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N - 4 - metil - N - (fenilmetil) benzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

N - {3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilfenil} - 3 - fluoro - 4 - metilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - propilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - propilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - (1 - metiletil) benzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - 1,3 - tiazol - 2 - ilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metil - N - 1,3 - tiazol - 2 - ilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N,N - 4 - trimetilbenzamida

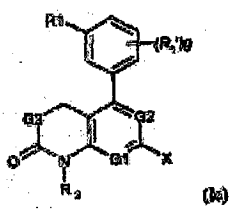
3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N,N - 4 - trimetilbenzamida

3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N, - 4 - dimetilbenzamida

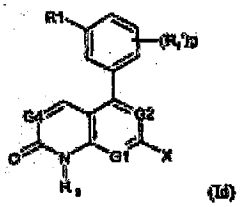
3 - [8 - (2,6 - difluorofenil) - 2 - (metilsulfonil) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - N, - 4 - dimetilbenzamida

ácido 3 - [8 - (2,6 - difluorofenil) - 2 - (metiltio) - 7 - oxo - 5,6,7,8 - tetrahidropirimido - [4,5 - d]pirimidin - 4 - il] - 4 - metilbenzoico.

84. Un compuesto de la formula:



(Ia)



(Id)

en donde

G1, y G2 son independientemente nitrógeno;

G3 es NH;

G4 es nitrógeno;

R1 es C (Z) N (R10') (CR10R20) vRb, C (Z) O (CR10R20) vRb, N (R10') C (Z) (CR10R20) vRb; N (R10') C (Z) N (R10') (CR10R20) vRb; o N (R10'=OC (Z) (CR10R20) vRb;

R1' es independientemente seleccionado en cada ocurrencia a partir de halógeno, C1 - 4alquilo, C1 - 4alquilo halo - sustituido, ciano, nitro, (CR10R20) v'NRdRd', (CR10R20) v'C (O) R12, SR5, S (O) R5, S (O) 2R5, o (CR10R20) v'OR13;

Rb es hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 10 alquilo, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10 alquilo, heterocíclilo, o heterociclilC1 - 10 alquilo , tales fracciones excluyendo hidrógeno, pueden todas ser opcionalmente susituidas;

X es R2, OR2', S (O) mR2', (CH2) n'N (R10') S (O) mR2', (CH2) n'N (R10') C (O) R2', (CH2) n'NR4R14, (CH2) n'N (R2') (R2'') , o N (R10') - Rh - NH - C (=N - CN) NRqRq';

X1 es N (R11) , O, S (O) m, o CR10R20;

Rh es seleccionado de un C1 - 10alquilo opcionalmente sustituido, - CH2 - C (O) - CH2 - , - CH2 - CH2 - O - CH2 - CH2 - , - CH2 - C (O) N (R10') CH2 - CH2 - , - CH2 - N (R10') C (O) CH2 - , - CH2 - CH (OR10') - CH2, - CH2 - C (O) O - CH2 - CH2 - , o –CH2 - CH2 - O - C (O) CH2 - ;

Rq y Rq' son independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquiloC1 - 10alquilo, C5 - 7cicloalquenilo, C5 - 7cicloalquinilo - C1 - 10alquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde todas las fracciones, excluyendo hidrógeno, son opcionalmente sustituidas, o Rq y Rq' junto con el nitrógeno al cual están fijadas formar un anillo opcionalmente sustituido de 5 a 7 miembros, tal anillo puede contener un heteroátomo adicional seleccionado de oxigeno, nitrógeno o azufre;

R2 es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

R2 es la fracción (CR10R20) q'X1 (CR10R20) qC (A1) (A2) (A3) , o (CR10R20) q'C (A1) (A2) (A3) ;

R2' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir;

R2'' es hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilalquilo, arilo, arilC1 - 10 alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, o una fracción de heterociclilC1 - 10alquilo, en donde estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o

en donde R2'' es la fracción (CR10R20) tX1 (CR10R20) qC (A1) (A2) (A3) ;

A1 es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A2 es es un C1 - 10 alquilo, heterociclilo, C1 - 10 alquilo heterocíclico, heteroarilo, heteroaril C1 - 10 alquilo, arilo, o arilC1 - 10 alquilo opcionalmente sustituido;

A3 es hidrógeno o es C1 - 10 alquilo opcionalmente sustituido;

R3 esC1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquil C1 - 10 alquilo, arilo, arilC1 - 10 alquilo, heteroarilC1 - 10alquilo, o una fracción de heterociclilC1 - 10alquilo, y en donde cada una de estas fracciones se pueden opcionalmente sustituir;

R4 y R14 son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno, C1 - 10alquilo, C3 - 7cicloalquilo , C3 - 7cicloalquilC1 - 4alquilo, arilo, arilC1 - 4 alquilo, heteroarilo, heterociclilo,C1 - 4 alquilo heterocíclico, heteroarilo o una fracción de

heteroaril C1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o R4 y R14 junto con el nitrógeno al cual están unidos formar un anillo heterocíclico opcionalmente sustituido de 4 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de oxigeno, azufre o nitrógeno;

R4' y R14' son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno o C1 - 4 alquilo, o R4' y R14' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico de 5 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de NR9';

R5 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, c2 - 4 alquenilo, C2 - 4 alquinilo, o NR4'R14', excluyendo las fracciones SR5 siendo SNR4'R14', S (O) 2R5 siendo SO2H y S (O) R5 siendo SOH;

R9' es seleccionado independientemente en cada ocurrencia a partir de hidrógeno, o C1 - 4alquilo;

R10 y R20 son independientemente seleccionados en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R10' es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R11 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno o C1 - 4alquilo;

R12 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

R13 es independientemente seleccionado en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C1 - 4alquilo halo sustituido, C2 - 4 alquenilo, C2 - 4 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenilo C1 - 4alquilo, arilo, arilC1 - 4alquilo, heteroarilo, heteroarilC1 - 4alquilo, heterociclilo, o una fracción de heterociclilC1 - 4 alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden sustituir opcionalmente;

Rd y Rd' son cada uno independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 4 alquilo, C3 - 6 cicloalquilo, C3 - 6 cicloalquilC1 - 4alquilo, y en donde cada una de estas fracciones, excluyendo hidrógeno se pueden opcionalmente sustituir; o Rd y Rd' junto con el nitrógeno al cual están unidas forman un anillo heterocíclico opcionalmente sustituido de 5 a 6 miembros, tal anillo opcionalmente puede contener un heteroátomo adicional seleccionado de oxigeno, azufre o NR9';

g es 0 o un entero con un valor de 1, 2, 3 o 4;

n' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 a 10;

m es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 0 2;

q es 0 o un entero con un valor de 1 a 10;

q' es 0, o un entero con un valor de 1 a 6;

t es un entero con un valor de 2 a 6;

v es 0 o un entero con un valor de 1 o 2;

v' es independientemente seleccionado en cada ocurrencia de 0 o un entero con un valor de 1 o 2;

Z es independientemente seleccionado en cada ocurrencia de oxigeno o azufre; o una sal farmacéuticamente aceptable, solvato o derivado fisiológicamente funcional.

85. El compuesto según la reivindicación 81 el cual es la Formula (Id) , o una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable.

86. El compuesto según la reivindicación 81 el cual es la formula (Id) , o una sal, solvato o derivado fisiológicamente funcional del mismo farmacéuticamente aceptable.

87. El compuesto según cualquiera de las reivindicaciones 84 a 86 en donde R1 es C (Z) N (R10') (CR10R20) vRb.

88. El compuesto según la reivindicación 84 en donde Rb es un heteroarilo, heteroarilalquilo, heterociclilo, o heterociclilalquilo opcionalmente sustituido.

89. El compuesto según la reivindicación 88 en donde Rb es un heteroarilo, o heteroarilalquilo opcionalmente sustituido.

90. Un compuesto según la reivindicación 84 en donde Rb es un 1,3 - tiazol - 2 - ilo, 5 - metil - 1,3 - tiazol - 2 - ilo, isoquinolina, 3 - tiofeno, indolo - 5ilo, piridin - 3 - ilo, piridina - 4 - ilo, indazolilo, benzotiazolo, 2 - metil - 1,3 - benzotiazol - 5 - ilo, pirazol - 3 - ilo, 4 - morfolino, 2 - furanilo, 2 - furanilmetilo, 2 - tienilo, 2 - tienilmetilo, tetrahidro - 2H - piran - 4ilo, tetrahidro - 2H - piran - 4ilo - metilo, tetrahidro - 2 - furanilo, otetrahidro - 2 - furanilmetilo, 2,3 - dihidro - 1,4 - benzodioxin - 6 - ilo, 1H - imidazol - 4 - ilo o 1H - imidazol - 4 - il - etilo.

91. El compuesto según la Reivindicación 84 en donde Rb es ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, o ciclopentilmetilo.

92. El compuesto según la Reivindicación 84 en donde el R1' es independientemente seleccionado de halógeno, C1 - 4 alquilo, o C1 - 4 alquilo halo - sustituido.

93. El compuesto según la reivindicación 92 en donde los sustituyentes son independientemente fluor, metilo, o CF3.

94. El compuesto según la Reivindicación 84 o 92 en donde g es 1.

95. El compuesto según cualquiera de las Reivindicaciones 81 a 83 en donde X es (CH2) nNR4R14, o (CH2) nN (R2') (R2'').

96. El compuesto según la Reivindicación 95 en donde X es (CH2) nNR4R14, y R4 y R14 son independentemente seleccionados de hidrógeno, C1 - 10 alquilo opcionalmente sustituido, arilo alquilo opcionalmente sustituido, aril - C1 - 4 alquilo opcionalmente sustituido, heterociclilo opcionalmente sustituido, heterociclil - C1 - 4 alquilo opcionalmente sustituido, heteroarilo opcionalmente sustituido o heteroarilC1 - 4 alquilo opcionalmente sustituido.

97. El compuesto según la reivindicación 93 en donde el C1 - 10 alquilo se puede sustituir una o más veces, independientemente en cada ocurrencia con NR4'R14'; halógeno, hidroxilo, alcoxilo, C (O) NR4'R14'; o NR4'C (O) C1 - 10alquilo.

98. El compuesto según la Reivindicación 95 en donde X es (CH2) nNR4R14 y uno entre R4 y R14 es un heteroaril - C1 - 4 alquilo opcionalmente sustituido, y la fracción de heteroarilo es seleccionada de tienilo, pirrolilo, oxazolilo, tiazolilo, isoxazolilo, isotiazolilo, imidazolilo, pirazolilo, triazolilo, piridazinilo, pirimidinilo, pirazinilo, benzoxazolilo, benzimidazolilo, y benzotiazolilo.

99. El compuesto según la Reivindicación 95 en donde X es (CH2) nNR4R14 y uno entre R4 y R14 es una fracción heterociclil - C1 - 4 alquilo seleccionada de tetrahidropirrola,

tetrahidropirano, tetrahidrofurano, pirrolinilo, pirrolidinilo, imidazolinilo, indolinilo, pirazolinilo, pirazolidinilo, piperidinilo, diazepinilo, piperazinilo, y morfolino.

100. El compuesto según la Reivindicación 95 en donde X es (CH2) nNR4R14 y R4 y R14 junto con el nitrógeno ciclizan para formar un anillo opcionalmente sustituido seleccionado de pirrolidina, piperidina, piperazina, y morfolina.

101. El compuesto según la Reivindicación 92 en donde el anillo R4 y R14 ciclizado es opcionalmente sustituido una o más veces independientemente por un alquilo opcionalmente sustituido, un arilo opcionalmente sustituido, un heteroarilo opcionalmente sustituido, un heterociclilo opcionalmente sustituido, (CR10R20) nN (R10') C (Z) OR7, o NR4'R14'.

102. El compuesto según la Reivindicación 101 en donde los sustituyentes opcionales son seleccionados de fenilo, pirrolidinilo, morfolino, piperazinilo, 4 - metil - 1 - piperazinilo, piperidinilo, 2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - ilo, 5 - cloro - 2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - ilo, difenilmetilo, metilo, etilo, propilo, butilo, amino, metilamino, y dimetilamino.

103. El compuesto según la reivindicación 84 en donde X es R2 y R2 es un anillo heterociclilo o heterociclilalquilo opcionalmente sustituido una o más veces independientemente en cada ocurrencia por un heterociclilo opcionalmente sustituido, heterociclil - c1 - 10 alquilo, arilo, aril - C1 - 10 alquilo, C1 - 10 alquilo, (CR10R20) nNReRe', o (CR10R20) nN (R10') C (Z) OR7.

104. El compuesto según la reivindicación 103 en donde R2 es seleccionado de 1,4` - bipiperin - 1 - ilo, 4 - metil - 1,4` - bipiperin - 1 - ilo, 4 - piperidinilamino, 4 - amino - 1 - piperidinilo, 2,2,6,6 - tetrametil - 4 - piperidinil) amino, 4 - metil - 1 - piperazinilo, (4 - morfolinil) - 1 - piperidinilo, (4 - metil - 1 - piperazinil) - 1 - piperidinilo, 4 - etil - 1 - piperazinilo, (2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - il) - 1 - piperidinilo, 5 - cloro - (2 - oxo - 2,3 - dihidro - 1H - benzimidazol - 1 - il) - 1 - piperidinilo, 4 - (1 - pirrolidinil) - 1 - piperidinilo, 4 - metilhexahidro - 1H - 1,4 - diazepin - 1 - ilo, 4 - propil - 1 - piperazinilo, o 4 - butil - 1 - piperazinilo.

105. El compuesto según la reivindicación 84 en donde R2 es sustituido una o más veces, independientemente en cada ocurrencia con C1 - 10alquilo, C1 - 10alquilo halo - sustituido, C2 - 10 alquenilo, C2 - 10 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquilC1 - 10alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 10alquilo, halógeno, - C (O) , ciano, nitro, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, heterociclilC1 - 10alquilo, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN,

(CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR10 R20) nOC (Z) R6, (CR10 R20) nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7.

106. El compuesto según la Reivindicación 105 en donde R2 es un alquilo opcionalmente sustituido.

107. El compuesto según la Reivindicación 106 en donde el C1 - 10 alquilo es opcionalmente sustituido por (CR10R20) nC (Z) OR6, (CR10R20) nOR6, o (CR10R20) nNR4R14.

108. El compuesto según cualquiera de las Reivindicaciones 84 a 86 en donde R2 es (CR10R20) q'X1 (Cr10R20) qC (A1) (A2) (A3) , o (CR10R20) q'C (A1) (A2) (A3) .

109. El compuesto según la reivindicación 108 en donde X1 es oxigeno o N (R10') .

110. El compuesto según la Reivindicación 109 en donde al menos uno entre A1, A2 o A3 es sustituido por (CR10R20) nOR6, q es 1 o 2, y q' es 0.

111. El compuesto según la Reivindicación 84 en donde X es (CH2) nN (R2') (R2'') , y R2' es un C1 - 10 alquilo opcionalmente sustituido, heterociclilo, heterociclilC1 - 10 alquilo, heteroarilalquilo.

112. El compuesto según la Reivindicación 84, o 111 en donde las fracciones R2' excluyendo hidrógeno son sustituidas 1 a 4 veces independientemente en cada ocurrencia por C1 - 10alquilo, C1 - 10alquilo halo - sustituido, C2 - 10 alquenilo, C2 - 10 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquil - C1 - 10alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 10alquilo, halógeno, - C (O) , ciano, nitro, arilo, arilC1 - 10alquilo, heteroarilo, heteroarilC1 - 10alquilo, heterociclilo, heterociclilC1 - 10alquilo, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN, (CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR-10 R20) nOC (Z) R6, (CR10 R20) nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7; en donde

R6 es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo; heterociclilo; heterociclilC1 - 10alquilo, arilo, arilC1 - 10alquilo, heteroarilo o heteroarilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno son opcionalmente sustituidas;

R7 es independientemente seleccionado en cada ocurrencia de C1 - 6 alquilo, arilo, aril - C1 - 6 alquilo, heterociclilo, heterociclilC1 - 6alquilo, heteroarilo, o heteroarilC1 - 6alquilo, y en donde cada una de estas fracciones se pueden sustituir de manera opcional;

Re y Re' son cada uno independientemente seleccionados en cada ocurrencia a partir de hidrógeno, C1 - 4alquilo, C3 - 7cicloalquilo, C3 - 7cicloalquilC1 - 4alquilo; arilo, aril - C1 - 4alquilo, heterociclilo, C1 - 4alquilo heterocíclico, heteroarilo o un heteroarilC1 - 4alquilo; o Re y Re' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico opcionalmente sustituido de 4 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de oxigeno, azufre o nitrógeno; y

en donde cada una de estas fracciones, excluyendo hidrógeno, se puede sustituir 1 a 4 veces, independientemente en cada ocurrencia por halógeno; hidróxilo; C1 - 10alquilo hidroxilo sustituido; C1 - 10alcoxilo; C1 - 10alcoxilo halo sustituido; amino, C1 - 4alquilamino mono - & di - sustituido; S (O) mRf; C (O) Rj; C (O) ORj; (CR10R20) nN (R10') C (Z) OR7; (CR10R20) nN (R10') C (Z) NRdRd'; C (O) NR4'R14'; NR4'C (O) C1 - 10alquilo; NR4'C (O) arilo; ciano; nitro, C1 - 10alquilo; C3 - 7cicloalquilo; C3 - 7cicloalquilC1 - 10alquilo; C1 - 10alquilo halo sustituido; arilo, arilC1 - 4alquilo, heterociclilo, C1 - 4alquilo heterocíclico, heteroarilo, o heteroC1 - 4alquilo, y en donde estos arilo, heterociclilo, y heteroarilo que contienen fracciones se pueden sustituir opcionalmente una o dos veces independientemente en cada ocurrencia por halógeno, C1 - 4alquilo, hidroxilo,g C1 - 4alquilo hidroxilo - sustituido, C1 - 10alcoxilo, S (O) malquilo, amino, C1 - 4alquilamino mono - &di - sustituido, C1 - 4alquilo, o CF3;

Rf es independientemente seleccionado en cada ocurrencia de C1 - 10alquilo, arilo, aril - C1 - 10alquilo, heteroarilo, heteroaril - C1 - 10alquilo, heterociclilo, o una fracción C1 - 10alquilo heterocíclico, y en donde estas fracciones se pueden todas opcionalmente sustituir;

R4' y R14' son cada una independientemente seleccionadas en cada ocurrencia de hidrógeno o C1 - 4 alquilo, o R4' y R14' junto con el nitrógeno al cual están fijados forman un anillo heterocíclico de 5 a 7 miembros, tal anillo opcionalmente contiene un heteroátomo adicional seleccionado de NR9';

Rj es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 4alquilo, arilo, aril - C1 - 4alquilo, heteroarilo, heteroaril - C1 - 4alquilo, heterociclilo, o una fracción C1 - 4alquilo heterocíclico, y en donde estas fracciones excluyendo hidrógeno se pueden todas opcionalmente sustituir; y

n es 0 o un entero con un valor de 1 a 10, y es independientemente seleccionado en cada ocurrencia.

113. El compuesto según la Reivindicación 84 o 112 en donde R2' es un anillo heterocíclico o heterociclilalquilo sustituido una o más veces, independientemente por C1 - 10 alquilo, arilo, arilalquilo, (CR10R20) nNReRe', o (CR10R20) nN (R10') C (OR7.

114. El compuesto según la Reivindicación 84 en donde la fracción (CH2) nN (R2'9 (R2'') es 1 - (fenilmetil) - 4 - piperidinamina, 2 - [4 - (fenilmetil) - 1 - piperazinil]etilamina, 2 - (1 - piperidinil) etilamina, 2 - (1 - metil - 2 - pirrolidin) etilamina, 2 - (1 - metil - 2 - pirrolidin) etilamina, 1 - [(fenilmetil) - 3 - pirrolidin]amina, 3 - [(1 - pirrolidin) propil]amina, 3 - [(hexahidro - 1H - azepin - 1 - il) propil]amina, (1 - metil - 4 - piperidinil) amina, 2 - [(4 - morfolinil) etil]amina, 2 - [(1 - pirrolidinil) etil] - amina, o [(1 - etil - 2 - pirrolidinil) metil]amina.

115. El compuesto según la Reivindicación 113 en donde R2' es un C1 - 10 alquilo opcionalmente sustituido, sustituido por (CR10R20) nNReRe' o 8CR10R20) nNReRe'C1 - 4alquilNReRe'.

116. El compuesto según la reivindicación 115 en donde Re y Re' son independientemente seleccionado de metilo, etilo, isopropilo, n - butilo, o t - butilo.

117. El compuesto según la Reivindicación 84 en donde (CH2) nN (R2') (R2'') es 3 - (dimetilamino) propil (metil) amina, 3 - (dietilamino) propilamina, propilamina, (2,2 - dimetilpropil) amina, (2 - hidroxipropil) amino, 2 - (dimetilamino) etilamina, 2 - (dimetilamino) etil (metil) amina, 3 - (dimetilamino) propilamina, 2 - (metilamino) etilamino, [(1 - metiletil) amino]etilamina, 3 - (dietilamino) propilamina, 3 - (dibutilamino) propilamina, 3[(1 - metiletil) amino]propilamina, 3 - (1,1 - dimetiletil) aminopropilamina, 3 - (dimetilamino) - 2,2 - dimetilpropilamina, 4 - (dietilamino) - 1 - metilbutilamina, o 3 - [[3 - (dimetilamino) propil] - (metil) amina.

118. El compuesto según cualquiera de las reivindicaciones 84 a 86 en donde R3 es un C1 - 10 alquilo opcionalmente sustituido, C3 - 7 cicloalquilo, C3 - 7 cicloalquilalquilo, o arilo.

119. El compuesto según la Reivindicación 118 en donde R3 es opcionalmente sustituido una o más veces, independientemente en cada ocurrencia, con C1 - 10alquilo, C1 - 10alquilo halo - sustituido, C2 - 10 alquenilo, C2 - 10 alquinilo, c3 - 7 cicloalquilo, C3 - 7cicloalquil - C1 - 10alquilo, C5 - 7 cicloalquenilo, C5 - 7 cicloalquenil C1 - 10alquilo, halógeno, ciano, nitro, (CR10R20) nOR6, (CR10R20) nSH, (CR10 R20) nS (O) mR7, (CR10 R20) nN (R10'') S (O) 2R7, (CR10 R20) nNReRe', (CR10 R20) nNReRe' C1 - 4alkylNReRe', (CR10 R20) nCN, (CR10 R20) nS (O) 2NReRe', (CR10 R20) nC (Z) R6, (CR10 R20) nOC (Z) R6, (CR10 R20)

nC (Z) OR6, (CR10 R20) nC (Z) NReRe', (CR10 R20) nN (R10') C (Z) R6, (CR10 R20) nN (R10') C (=N (R10')) NReRe', (CR10 R20) nC (=NOR6) NReRe', (CR10 R20) nOC (Z) NReRe', (CR10 R20) nN (R10') C (Z) NReRe', or (CR10 R20) nN (R10') C (Z) OR7; y en donde R6 es independientemente seleccionado en cada ocurrencia de hidrógeno, C1 - 10 alquilo, C3 - 7cicloalquilo; heterociclilo; heterociclilC1 - 10alquilo, arilo, arilC1 - 10alquilo, heteroarilo o heteroarilC1 - 10alquilo, en donde cada una de estas fracciones, excluyendo hidrógeno son opcionalmente sustituidas;

R7 es independientemente seleccionado en cada ocurrencia de C1 - 6 alquilo, arilo, aril - C1 - 6 alquilo, heterociclilo, heterociclilC1 - 6alquilo, heteroarilo, o heteroarilC1 - 6alquilo, y en donde cada una de estas fracciones se pueden sustituir de manera opcional;

n es 0 o un entero con un valor de 1 a 10, y es independientemente seleccionado en cada ocurrencia.

120. El compuesto según la Reivindicación 120 en donde el R3 es un arilo opcionalmente sustituido.

121. El compuesto según la Reivindicación 120 en donde el arilo es un fenilo sustituido una o más veces independientemente en cada ocurrencia por halógeno, (CR10R20) nOR6, C1 - 10 alquilo, (CR10R20) nNR16R26, o alquilo halo - sustituido.

122. El compuesto según la Reivindicación 121 en donde el fenilo es sustituido una o más veces independientemente por halógeno, hidroxilo, alcoxilo, amino, alquilo, o CF3.

123. El compuesto según la Reivindicación 122 en donde el fenilo es disustituido una o más veces independientemente por halógeno.

124. El compuesto según la Reivindicación 123 en donde el anillo fenilo es sustituido una o más veces independientemente por halógeno.

125. El compuesto según la Reivindicación 124 en donde R3 es un 2,6 - difluorofenilo.

126. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable del mismo según la Reivindicación 84 y un vehículo o diluyente farmacéuticamente aceptable.

127. Una composición farmacéutica que comprende una cantidad efectiva de un compuesto, o sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable según la reivindicación 84, y en mezcla con uno o más vehículos, diluyentes o excipientes farmacéuticamente apropiados, para administración por vía intravenosa, intramuscular, subcutánea, intranasal, inhalación oral, intrarectal, intravaginal o intraperitoneal.

128. Un método para tratar con componente inflamatorio de una enfermedad mediada por un CSBP/RK/p38 en un mamífero en necesidad del mismo, tal método comprende administración a dicho mamífero de una cantidad efectiva de un compuesto, una sal, solvato o derivado fisiológicamente funcional farmacéuticamente aceptable del mismo, según la reivindicación 84.

129. El método según la reivindicación 128 en donde la enfermedad mediada por CSBP/RK/p38 es artritis soriática, síndrome de Reiter, gota, artritis traumática, artritis rubeola, sinovitis aguda, artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa, y otra condición artrítica, sepsis, choque séptico, choque endotóxico, sepsis gram negativa, síndrome de choque tóxico, malaria cerebral, meningitis, ataque isquémico y hemorrágico, neurotrauma/lesión de cabeza cerrada, asma, síndrome de distrés respiratorio en el adulto, enfermedad inflamatoria pulmonar crónica, enfermedad pulmonar obstructiva crónica (COPD) , silicosis, sarcososis pulmonar, enfermedad de resorción ósea, osteoporosis, restenosis, lesión por reperfusión cardiaca y cerebral y renal, falla cardiaca congestiva, cirugía de bypass arterial coronario (CABG) , trombosis, glomerulonefritis, falla renal crónica, diabetes, retinopatía diabética, degeneración macular, aterosclerosis, retinopatía diabética, degeneración macular, crecimiento tumoral y metástasis, enfermedad angiogénica, neumonía inducida por influencia, eczema, dermatitis de contacto, soriasis, quemadura solar, o conjuntivitis.

130. Un método para tratar inflamación en un mamífero en necesidad del mismo que comprende administración a dicho mamífero de una cantidad efectiva de un compuesto según la reivindicación 84.

132. Un método para tratar artritis traumática, artritis rubeola, sinovitis aguda, artritis reumatoide, espondilitis reumatoide, osteoartritis, artritis gotosa y otra condición artrítica, en un mamífero en necesidad del mismo, comprendiendo administración a dicho mamífero de una cantidad efectiva de un compuesto según la reivindicación 84.

133. Un método para tratar asma, síndrome de distrés respiratorio adulto, enfermedad inflamatoria pulmonar crónica, enfermedad pulmonar obstructiva crónica (COPD) en un mamífero en necesidad del mismo, que comprende administración a dicho mamífero de una cantidad efectiva de un compuesto según la reivindicación 84.

134. Un método para tratar aterosclerosis, enfermedad intestinal inflamatoria, enfermedad de Crohn, colitis ulcerativa, en un mamífero en necesidad del mismo, comprendiendo administración a dicho mamífero de la cantidad efectiva de un compuesto según la reivindicación 84.

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Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

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- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
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COMPLETA [ ] INCOMPLETA [ ]

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

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	Solicitud internacional	PCT/US2006/010792
	Fecha inicio fase nacional	25/10/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13819

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. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

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 02 NOV 2007
adpa11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU61344	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US06/10792	International filing date (*day/month/year*) 24 March 2006 (24.03.2006)	(Earliest) Priority Date (*day/month/year*) 25 March 2005 (25.03.2005)
Applicant GLAXO GROUP LIMITED		

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

This international search report consists of a total of 2 sheets.

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

1. **Basis of the Report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed.
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. ☒ **Certain claims were found unsearchable** (See Box No. II)
3. ☐ **Unity of invention is lacking** (See Box No. III)
4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. ____
      ☐ as suggested by the applicant.
      ☐ as selected by this Authority, because the applicant failed to suggest a figure.
      ☐ as selected by this Authority, because this figure better characterizes the invention.
   b. ☐ none of the figures is to be published with the abstract.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/10792

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☒ Claims Nos.: 131
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 131 is not listed in the claims

3. ☒ Claims Nos.: 50,71-74,113,115 and 116
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US06/10792

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07D 475/00**(2007.01),**413/12**(2007.01),**413/14**(2007.01),**243/08**(2007.01);**A61K 31/519**(2007.01),**31/535**(2007.01),**31/55**(2007.01),**31/5513**(2007.01)
C07D 239/47(2007.01)

USPC: 544/257,258,118,317;540/575,600;514/262.1,234.2,217.06,218

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/257,258,118,317;540/575,600;514/262.1,234.2,217.06,218

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS online, East inventor search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/0100756 A1 (ADAMS et al) 29 May 2003 (29.05.2003), entire document.	1-49, 51-70, 75-112, 114, 117-130, 132-134
A	WO 2006/065703 A1 (OSLOB et al) 22 June 2006 (22.06.2006), entire document.	1-49, 51-70, 75-112, 114, 117-130, 132-134

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
08 November 2006 (08.11.2006)

Date of mailing of the international search report
23 FEB 2007

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Mark L. Berch
Art Unit 1624
Telephone No. (571) 272-9046

Felicia D. Roberts for

Form PCT/ISA/210 (second sheet) (April 2005)

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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
DARA L. DINNER
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	23 FEB 2007
Applicant's or agent's file reference PU61344	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US06/10792	24 March 2006 (24.03.2006)	25 March 2005 (25.03.2005)

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

IPC: Please See Continuation Sheet
USPC: 544/257,258,118,317;540/575,600;514/262.1,234.2,217.06,218

Applicant

GLAXO GROUP LIMITED

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

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☒ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	09 November 2006 (09.11.2006)	Mark L. Berch, Art unit 1624 Telephone No. (571) 272-9046

Form PCT/ISA/237 (cover sheet) (April 2005)

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/10792

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/10792

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 50,71-74,113,115,116 and 131

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 50,71-74,113,115,116 and 131 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 50,71-74,113,115 and 116 are improper multiple dependent claims under PCT Rule 6.4(a). A multiple dependent claim cannot depend upon another multiple dependent claim. Claim 131 is not listed in the claims.

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

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

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/10792

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-49,51-70,75-112,114,117-130 and 132-134	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-49,51-70,75-112,114,117-130 and 132-134	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-49,51-70,75-112,114,117-130 and 132-134	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-49, 51-70, 75-112, 114, 117-130 and 132-134 meet *the* criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest compounds of formula (I) or (Ia) which have the required substitution of R1 on the phenyl ring at the 4-position of the di-1,3-pteridine bicycle.

Claims 1-49, 51-70, 75-112, 114, 117-130 and 132-134 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in the pharmaceutical industry.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US06/10792

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 75 and 77-79 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: claim 75 does not further limit claim 1. Thus claims 77 and 78, which are drawn to compositions, and claim 79, which is drawn to a method of treatment, does not further limit claims 65-67. The utility of said compositions is not given patentable weight.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US06/10792

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 1-49,51-62,65-70,75-112 and 114-134 objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 1-49,51-62,65-70,75-112 and 114-134 are indefinite for the following reason(s): the term "physiologically functional derivates" is vague. What are these "physiologically functional derivates?" Are these the same across species?

Claims 1-49,51-62,65-70,75-112 and 114-134 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims 1-49,51-62,65-70,75-112 and 114-134 are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: The claims are drawn to solvates. But the numerous examples presented all failed to produce a solvate. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claims 67-70, 79 and 128-134 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 67-70, 79 and 128-134 indefinite for the following reason(s): the elaborate lists of diseases cited in said claims occur by different mechanisms of actions and at different locations in the body. And thus, cannot be treated by any one drug.

Claim 34 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 34 indefinite for the following reason(s): the definition of "NreRe'" is not in claim 1, from which claim 34 depends.

Claim 42 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 34 indefinite for the following reason(s): the definition of "...OR6" is only defined in claim 37, to which claim 42 does not depend.

Claim 59 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 34 indefinite for the following reason(s): Formula (Ic) is not defined in claim 58 or claim 1, from which it depends.

Claims 75 and 77-79 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 34 indefinite for the following reason(s): claim 75 is the same in scope as claim 1 and thus does not further limit claim 1. Claims 77 and 78, which are drawn to compositions, and claim 79, which is drawn to a method of treatment, do not further limit claims 65-67. The utility of said compositions is not given patentable weight.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US06/10792

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Continuation of IPC:
C07D 475/00(2007.01),**413/12**(2007.01),**413/14**(2007.01),**243/08**(2007.01);**A61K 31/519**(2007.01),**31/535**(2007.01),**31/55**(2007.01),**31/5513**(2007.01)
C07D 239/47(2007.01)