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Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTAR

09-127785

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS AMINO-HETEROCÍCLICOS

SOLICITANTE: PFIZER INC

DIRECCIÓN: 235 East 42nd Street, New York, NY 10017, E. U. A.

624

APODERADO: CARLOS R. OLARTE

BOGOTÁ 10 de Noviembre de 2009

P2009/000185

OLARTE RAISBECK

OLARTE RAISBECK MC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-127785- -00000-0000
Fecha: 2009-11-10 16:57:44 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 405

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000185**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: PFIZER INC
Dirección: 235 East 42nd Street, New York, NY 10017 E.U.A
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
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 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: 1. Patrick Robert VERHOEST; 2. Caroline PROULX-LAFRANCE,
Dirección: Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340
Nacionalidad o Domicilio: 1. Estadounidense 2. Canadiense

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2008/001125 Fecha Mayo 5, 2008

Publicación Internacional No. WO 2008/139293 Fecha Noviembre 20, 2008

(6) **Título (54)** **COMPUESTOS AMINO-HETEROCÍCLICOS** (Folio 504)

Clasificación Internacional (51) C07D 487/04

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Mayo 11, 2007	60/917,333

(9) **Comprobante de pago No.** 09-83,938 **Fecha** Noviembre 9, de 2009

(10) **ANEXOS**

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-018.680
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones.
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
	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.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA

C.C. 79.782.747 Btá T.P. 74.295

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 83,938
FECHA : NOVIEMBRE 9 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-127785- -00000-0000
Fecha: 2009-11-10 16:57:44 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 405

***** 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 DE BOGOTA	062754387	168355983	09/11/2009	3,476,000.00

***** 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	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA 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

PFIZER INC.

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

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

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

Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

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

CERTIFICADO

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117

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OLARTE RAISBECK & FRIERI, LTDA.
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Power of Attorney

The undersigned,

domiciled in

Pfizer Inc.

235 East 42nd Street, New York, NY 10017 USA

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,

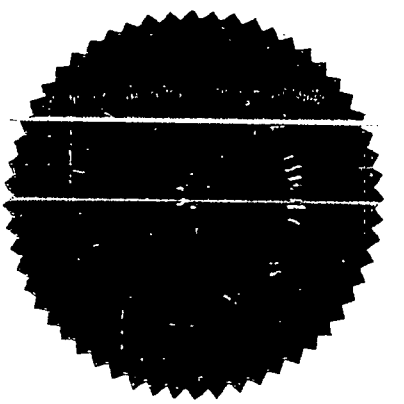
domiciliado en

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

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



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Notarial Certification

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

1. That J. Trevor Lumb

of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in
New York, New York, U.S.A.
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

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

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

4. Que
con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Epsom In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

APOSTILLE

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

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

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

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

5. at London/à Londres — Certified/Attesté

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

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

8. Number/sous No **G210434**

9. Stamp: / timbre:

10. Signature: **R. Bawden**

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

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

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

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International Bureau

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20 November 2008 (20.11.2008)

PCT

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(71) Applicant *(for all designated States except US)*: **PFIZER INC.** [US/US]; 235 East 42nd, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VERHOEST, Patrick, Robert** [US/US]; Pfizer Global Research & Development, Eastern Point Road, Groton, CT 06340 (US). **PROULX-LAFRANCE, Caroline** [CA/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agent: **FULLER, Grover, F., Jr.**; Pfizer Inc., 150 East 42nd Street, New York, NY 10017 (US).

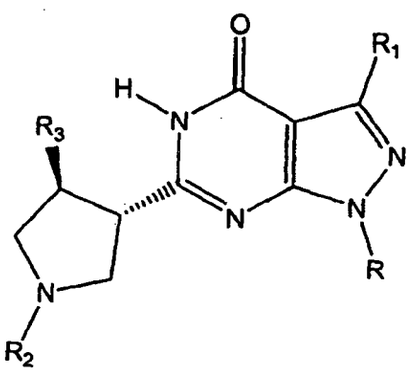
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

WO 2008/139293 A1

(54) Title: AMINO-HETEROCYCLIC COMPOUNDS



(I)

(57) Abstract: The invention provides PDE9-inhibiting compounds of Formula (I), and pharmaceutically acceptable salts thereof, wherein R, R_1, R_2 and R_3 are as defined herein. Pharmaceutical compositions containing the compounds of Formula I, and uses thereof in treating neurodegenerative and cognitive disorders, such as Alzheimer's disease and schizophrenia, are also provided.

AMINO-HETEROCYCLIC COMPOUNDS

RELATED APPLICATION

This application claims the benefit under 35 U.S.C. §119(e) of U.S. provisional application Ser. No. 60/917,333, filed June 11, 2007.

FIELD OF THE INVENTION

This invention relates to a series of novel compounds that are selective inhibitors of phosphodiesterase type 9 ("PDE9"). More particularly, the invention relates to pyrazolo[3,4-d]pyrimidinone compounds for use in the treatment and prevention of neurodegenerative diseases and other diseases and disorders influenced by modulation of PDE9.

BACKGROUND OF THE INVENTION

Cyclic nucleotides cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) are important second messengers and thus are central to the control and regulation of a multitude of cellular events, both physiological and pathophysiological, in a wide variety of organs.

Cyclic GMP is formed from GTP by the catalytic reaction of guanylyl cyclase (GC), which is activated by nitric oxide (NO). Cyclic GMP in turn activates cGMP-dependent protein kinases (cGK), which mediate localized and global signaling. A variety of physiological processes in the cardiovascular, nervous and immune systems are controlled by the NO/cGMP pathway, including ion channel conductance, glycogenolysis, cellular apoptosis, and smooth muscle relaxation. In blood vessels, relaxation of vascular smooth muscles leads to vasodilation and increased blood flow.

The phosphodiesterase (PDE) enzyme family hydrolyses cGMP and cAMP. The PDE9 enzyme has been identified as a novel member of the PDE enzyme family that selectively hydrolyses cGMP over cAMP. *See* Fisher *et al.*, *J. Biol. Chem.*, 273(25), 15559-15564 (1998). PDE9 has been found to be present in a variety of human tissues, namely the testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen, as well as in smooth muscle cells within the human vasculature of a variety of tissues.

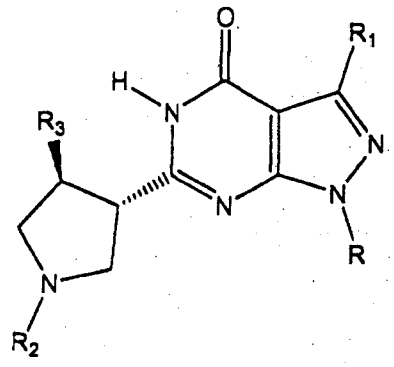
Recent studies have directly implicated dysfunction of NO/cGMP/cGK signaling in Alzheimer's disease. For example, disruption of Long Term Potentiation (LTP), a physiological correlate of learning and memory, by amyloid-ß peptide was shown to result from a malfunction of NO/cGMP signaling. Puzzo *et al.*, *J. Neurosci.*, 25(29):6887-6897 (2005). Moreover, in rats showing deficits in memory tasks due to depletion in forebrain acetylcholinesterase (which is associated with Alzheimer's disease), administration of a nitric oxide mimetic increased GC activity and reversed the cognitive deficits in memory tasks. Bennett *et al.*, *Neuropsychopharmacology*, 32:505-513 (2007). It is therefore believed that therapeutic agents capable of enhancing the GC/NO/cGMP/cGK signaling cascade may be useful as a new approach to the treatment of Alzheimer's disease and other neurodegenerative disorders.

By reducing or preventing the hydrolysis of cGMP by PDE9, PDE9 inhibitors elevate the intracellular level of cGMP, thus enhancing or prolonging its effects. It has been found that an increase in cGMP concentration in rats leads to improvement in learning and memory in social and object recognition tests. *See, e.g.*, Boess et al., *Neuropharmacology*, 47:1081-1092 (2004). Inhibition of PDE9 has been shown to increase LTP. Hendrix, *BMC Pharmacol.*, 5(Supp 1):55 (2005).

Accordingly, there is a need for PDE9 inhibitors that are effective in treating conditions that may be regulated or normalized by inhibition of PDE9.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I),



(I)

and pharmaceutically acceptable salts thereof, wherein R, R_1, R_2, and R_3 are as defined herein.

The present invention is also directed to compositions containing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent, and optionally further comprising a second pharmaceutical agent.

The present invention is further directed to a method of inhibiting PDE9 in a mammal in need of such inhibition, comprising the step of administering to the mammal a PDE9-inhibiting amount of a) a compound of Formula I, or a pharmaceutically acceptable salt thereof; or b) a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

The present invention is further directed to a method of treating a neurodegenerative disease in a mammal in need of such treatment, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention is further directed to a method of promoting neurorestoration in a mammal in need of such neurorestoration, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

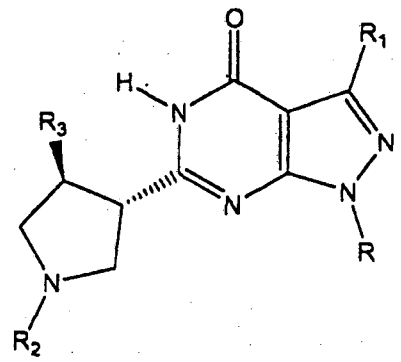
The present invention is still further directed to a method of improving cognitive deficits and treating cognitive impairment in a mammal in need of

such improvement or treatment, comprising the step of administering to the mammal a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

With the foregoing and other advantages and features of the invention that will become hereinafter apparent, the nature of the invention may be more clearly understood by reference to the following detailed description of the invention and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises novel selective PDE9 inhibitors of Formula (I),



(I)

and pharmaceutically acceptable salts thereof, wherein:

R is selected from the group consisting of (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo, and (C_1-C_4)haloalkyl.

R_1 is selected from the group consisting of hydrogen, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)haloalkyl, and cyclopropyl;

R_2 is selected from the group consisting of (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_1-C_6)haloalkyl, heteroaryl selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, and ER_5, wherein the

heteroaryl optionally may be substituted with one to three substituents independently selected from the group consisting of $(C_1$-$C_4)$alkyl and $(C_1$-$C_4)$haloalkyl;

R_3 is selected from the group consisting of hydrogen, $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_3$-$C_6)$cycloalkyl, and $(C_1$-$C_4)$haloalkyl;

E is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-C(O)-$;

R_5 is selected from the group consisting of $(C_3$-$C_8)$cycloalkyl, heterocycloalkyl, aryl, aryloxy, and heteroaryl, any of which optionally may be substituted with one to three substituents, such substituents being independently selected from the group consisting of $(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkenyl, $(C_2$-$C_4)$alkynyl, $(C_1$-$C_4)$hydroxyalkyl, $(C_1$-$C_4)$haloalkyl, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$haloalkoxy, $(C_3$-$C_8)$cycloalkyl, halo, cyano, phenyl, morpholinyl, $(C_1$-$C_4)$alkylamino, pyrazolyl, triazolyl, and imidazolyl.

Preferably, R is selected from the group consisting of ethyl, isopropyl, trifluoroethyl, cyclobutyl, cyclopentyl, difluorocyclohexyl, methoxyphenyl, and tetrahydro-2H-pyran-4-yl; R_1 is hydrogen or methyl; R_2 is methyl, trifluoroethyl, trifluorobutyl, pyrimidinyl, trifluoromethylpyrimidinyl, or ER_5; R_3 is methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, or cyclopropyl; E is $-CH_2-$ or $-C(O)-$; and R_5 is selected from the group consisting of substituted or unsubstituted cyclopentyl, morpholinyl, phenyl, naphthyl, benzyloxy, pyrimidinyl, pyridinyl, quinolinyl, quinoxalinyl, pyrazinyl, pyrazolyl, benzimidazolyl, cinnolinyl, naphthydrinyl, pyrido[2,3-b]pyrazinyl, imidazo[4,5-c]pyridinyl, benzothiadiazolyl, tetrahydropyrazolo[1,5-a]pyridinyl, dihydrobenzodioxinyl, imidazolyl, dihydrobenzofuranyl, triazolyl, oxazolyl, isoxazolyl, benzodioxinyl, thiazolyl, imidazo[1,2-a]pyridinyl, tetrahydrobenzothiazolyl, dihydrobenzoxazinyl, tetrahydropyranyl, tetrahydropyrazolo[1,5-a]azepinyl, and dihydropyrrolo[1,2-b]pyrazolyl.

More preferably, R is selected from the group consisting of isopropyl, cyclobutyl, cyclopentyl, and tetrahydro-2H-pyranyl; R_1 is hydrogen; R_2 is ER_5; R_3 is methyl or ethyl; E is $-CH_2-$; and R_5 is selected from the group

consisting of phenyl, pyrimidin-2-yl, pyridin-2-yl, pyrazin-2-yl, and 5-methylpyrazin-2-yl.

In other preferred embodiments, the compound is:

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-pyrimidin-2-ylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(trifluoromethyl)pyrimidin-2-yl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzoyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[3-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1,4-dimethylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-8-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(6-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-isopropylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-3-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-phenylethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(3-methylpyridin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-cyclopropylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinolin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-(trifluoromethyl)pyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-(1-benzylpyrrolidin-3-yl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-4-ethyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3,4-trans)-4-ethyl-1-[(6-methoxypyridin-3-yl)methyl]pyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-4-ethyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(cinnolin-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(quinoxalin-6-ylmethyl)-4-(trifluoromethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3S,4S)-1-{[2-(dimethylamino)pyrimidin-4-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-cyclopropyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-cyclopropyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-cyclopropyl-1-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-ethyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3,4-trans)-4-ethyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(4,4-difluorocyclohexyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2,2,2-trifluoroethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,5-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,8-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(pyrido[2,3-b]pyrazin-8-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3,4-trans)-1-[(6-methoxy-1,5-naphthyridin-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3,4-trans)-1-[(8-fluoroquinolin-2-yl)methyl]-4-methylpyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(v)-1-[(6-methoxyquinolin-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclobutyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3,4-trans)-4-ethyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclobutyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2,1,3-benzothiadiazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinoxalin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(3-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(35-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[4-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[(3S,4S)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[2-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-thiopyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[3-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(26-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-ethyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-ethyl-1-[(6-methoxypyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-ethyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-ethyl-1-(quinoxalin-2-ylcarbonyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-45-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile;

3-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-45-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile;

4-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-45-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[3-(1H-pyrazol-1-yl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyridin-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(2-chloro-6-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[2-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

1-cyclopentyl-6-{(3,4-trans)-1-[(2-ethoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[4-(1H-imidazol-1-yl)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-methoxy-3-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1-benzofuran-7-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(5-fluoro-2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-fluoro-4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-fluoro-4-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methyl-1,3-thiazol-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(4-isopropyl-1,3-thiazol-2-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-difluoro-4-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-{[6-(1H-pyrazol-1-yl)pyridin-2-yl]methyl}pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-naphthylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(2-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(1H-1,2,4-triazol-1-yl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-methoxy-4-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(1-naphthylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-fluoro-4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(5-methylisoxazol-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-fluoro-6-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-fluoro-3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(2-chloro-4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,4-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(4-chloro-2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-{[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl}benzonitrile;

1-cyclopentyl-6-[(3,4-trans)-1-(2,5-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2-{[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl}benzonitrile;

6-[(3,4-trans)-1-(3-chloro-4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[4-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(3-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(3-chloro-2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(1,3-thiazol-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-fluoro-2-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(2-ethylpyrimidin-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-isopropylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(1-ethyl-1H-pyrazol-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(4-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(isoxazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-{[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-phenyl-1,3-oxazol-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-isopropoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(cinnolin-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[3-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-fluoro-3-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(1H-pyrazol-1-yl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(2,7-dimethylimidazo[1,2-a]pyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(4-isopropoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-{[2-(1-hydroxy-1-methylethyl)pyridin-4-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(mesitylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,6-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

4-{[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl}benzonitrile;

1-cyclopentyl-6-[(3,4-trans)-1-(2-fluoro-5-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,6-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(3-phenylpropyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[2-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,4,4-trifluorobutyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(cyclopentylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,4-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(morpholin-4-ylmethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(2,1,3-benzothiadiazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3,4-trans)-1-[2-(benzyloxy)ethyl]-4-methylpyrrolidin-3-yl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,6-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(3,5,6-trimethylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,4-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1-benzofuran-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-methoxy-5-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(2-chlorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3,4-trans)-1-(2,1,3-benzothiadiazol-4-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-pro pylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-1-[(1-ethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[2-(trifluoromethoxy)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3,4-trans)-1-(3,5-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; or

1-cyclopentyl-6-[(3,4-trans)-1-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

or a pharmaceutically acceptable salt thereof.

The compounds of the invention have been surprising found to show pharmacological activity including in selectively inhibiting PDE9 that makes them suitable for the treatment, prevention and/or control of in treating conditions that may be regulated or normalized by inhibition of PDE9.

The compounds and intermediates of the present invention may be named according to either the IUPAC (International Union for Pure and Applied Chemistry) or CAS (Chemical Abstracts Service, Columbus, OH) nomenclature systems.

Definitions

Certain terms used herein are generally defined as follows:

The carbon atom content of the various hydrocarbon-containing moieties herein may be indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety. Thus, for example, (C_1-C_6)alkyl refers to an alkyl group of one to six carbon atoms inclusive.

The term "alkoxy" refers to a straight or branched, monovalent, saturated aliphatic hydrocarbon radical bonded to an oxygen atom that is attached to a core structure. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *tert*-butoxy, pentoxy, and the like.

The term "alkyl" means a saturated monovalent straight or branched aliphatic hydrocarbon radical. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, *sec*-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and the like.

The term "alkenyl" means a partially unsaturated straight or branched aliphatic hydrocarbon radical having one or more double bonds. Examples of alkenyl groups include ethenyl (also known as "vinyl"), allyl, 1-propenyl, isopropenyl, *n*-butenyl, *n*-pentenyl, and the like. The term "alkenyl" embraces radicals having "*cis*" and "*trans*" orientations, or alternatively, "*Z*" and "*E*" orientations.

The term "alkynyl" means a partially unsaturated straight or branched aliphatic hydrocarbon radical having one or more double bonds. Examples of

alkynyl groups include 1-propynyl, 2-propynyl (also known as "propargyl"), 1-butynyl, 2-butynyl, 1-pentynyl, and the like.

The term "aryl" denotes a monocyclic or polycyclic aromatic ring system, for example, anthracenyl, benzyl, fluorenyl, indenyl, naphthyl, phenanthrenyl, phenyl and the like. The term "aryl" is also intended to include the partially hydrogenated derivatives of such ring systems, e.g. 1,2,3,4-tetrahydronaphthyl.

The term "aryloxy" denotes an aryl radical bonded to an oxygen atom that is attached to a core structure, such as benzyloxy.

The term "cycloalkyl" denotes a saturated monocyclic or bicyclic cycloalkyl group. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "halogen" or "halo" represents chlorine, bromine, fluorine and iodine atoms and radicals.

The term "haloalkyl" refers to an alkyl or cycloalkyl substituent wherein at least one hydrogen radical is replaced with a halogen radical. Where more than one hydrogen is replaced with halogen, the halogens may be the same or different. Examples of haloalkyl radicals include trifluoromethyl, 2,2,2-trifluoroethyl, 4,4,4-trifluorobutyl, 4,4-difluorocyclohexyl, chloromethyl, dichloromethyl, trichloromethyl, 1-bromoethyl, and the like.

The term "haloalkoxy" refers to an alkoxy radical in which at least one hydrogen radical is replaced with a halogen radical. Where more than one hydrogen is replaced with halogen, the halogens may be the same or different. Examples of haloalkoxy radicals include difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, chloromethoxy, bromomethoxy, and the like.

The term "heteroaryl" as used herein includes heterocyclic unsaturated ring systems containing one or more heteroatoms such as nitrogen, oxygen, and sulfur. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. The heteroaryl radicals may be bonded via a carbon atom or a heteroatom. The term "heteroaryl" is also

intended to include the partially hydrogenated derivatives of such ring systems. Examples of heteroaryl groups include furanyl (also known as "furyl"), imidazolinyl, imidazolyl (also known as "1,3-diazolyl"), indolyl, oxadiazolyl, oxazinyl, oxazolyl, isoxazolyl, pyranyl, pyrazinyl (also known as "1,4-diazinyl"), pyrazolyl (also known as "1,2-diazolyl"), pyrazolinyl, pyrazyl, pyridazinyl (also known as "1,2-diazinyl"), pyridyl (also known as pyridinyl), pyrimidinyl (also known as "1,3 diazinyl" and "pyrimidyl"), pyrrolyl, thiadiazinyl, thiadiazolyl, thiatriazolyl, thiazolyl, isothiazolyl, thienyl, thiofuranyl (also known as "thiophenyl"), thiopyranyl, triazinyl, triazolyl, and the like.

The term "heteroaryl" also embraces radicals in which 2 or 3 rings are fused together, wherein at least on such ring contains a heteroatom as a ring atom, including radicals wherein (a) a heterocycloalkyl ring is fused with an aryl or heteroaryl ring, or (b) a cycloalkyl ring is fused with a heteroaryl ring. Examples of 2-fused ring heteroaryls include benzodioxinyl, dihydrobenzodioxinyl, benzofuranyl, dihydrobenzofuranyl, isobenzofuranyl, benzimidazolyl, benzothiadiazolyl, tetrahydrobenzothiadiazolyl, benzothiazolyl, benzothienyl (also known as "benzothiophenyl," "thionaphthenyl," and "benzothiofuranyl"), benzoxazinyl, dihydrobenzoxazinyl, benzoxazolyl, chromanyl, isochromanyl, chromenyl, cinnolinyl (also known as "1,2-benzodiazinyl"), imidazopyridinyl (e.g. imidazo[1,2-a]pyridinyl or imidazo[4,5-c]pyridinyl), indazolyl, indolinyl, isoindolinyl, indolizinyl, indolyl, isoindolyl, naphthyridinyl, oxathiolopyrrolyl, pteridinyl, pthalazinyl, purinyl (also known as "imidazo[4,5-d]pyrimidinyl"), pyranopyrrolyl, pyrazoloazepinyl, tetrahydropyrazoloazepinyl (e.g. tetrahydropyrazolo[1,5-a]azepinyl), pyrazolopyridinyl, tetrahydropyrazolopyridinyl (e.g. tetrahydropyrazolo[1,5-a]pyridinyl), pyrazolopyrimidinyl (e.g. pyrazolo[3,4-d]pyrimidinyl), pyridopyrazinyl (e.g. pyrido[2,3-b]pyrazinyl), pyridopyridinyl, pyrrolopyrazolyl, dihydropyrrolopyrazolyl (e.g. dihydropyrrolo[1,2-b]pyrazolyl), quinazolinyl (also known as "1,3-benzodiazinyl"), quinolinyl (also known as "1-benzazinyl"), isoquinolinyl (also known as "2-benzazinyl"), quinolizinyl, quinolyl, isoquinolyl,

quinoxalinyl, dithianaphthalenyl, thienofuranyl (e.g. thieno[3,2-b]furanyl), and the like.

Examples of 3-fused ring heteroaryls include acridinyl, diazaanthryl, triazaphenanthrene, carbazolyl, carbolinyl, furocinnolinyl, perimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, thianthrenyl, xanthenyl, and the like.

The term "heterocycloalkyl" denotes a saturated monocyclic or polycyclic cycloalkyl group, in which at least one of the carbon atoms is replaced with a heteroatom such as nitrogen, oxygen or sulfur. If the heterocycle contains more than one heteroatom, the heteroatoms may be the same or different. The heterocycloalkyl radicals may be bonded via a carbon atom or a heteroatom. Examples of heterocycloalkyl groups include azetidinyl, dioxacyclohexyl, 1,3-dioxolanyl, imidazolidinyl, morpholinyl, piperazinyl, piperidinyl, pyrazolidinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiazanyl, and the like.

A cyclic group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3- or 4-pyridyl (2-, 3-, or 4-pyridinyl).

The term "mammal" means animals including, for example, dogs, cats, cows, sheep, goats, horses and humans. Preferred mammals include humans.

The term "oxo" means a carbonyl group formed by the combination of a carbon atom and an oxygen atom.

The term "patient" includes both human and non-human patients.

The phrase "pharmaceutically acceptable" indicates that the designated carrier, vehicle, diluent, and/or salt is generally chemically and/or physically compatible with the other ingredients comprising the formulation, and physiologically compatible with the recipient thereof.

The term "salts" refers to both organic and inorganic salts of a compound of Formula (I). Such salts can be prepared *in situ* during the final

isolation and purification of a compound, or by separately reacting a compound, prodrug or stereoisomer of Formula (I) with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative anionic salts include hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitate, pamoate, malonate, stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and laurylsulphonate salts and the like. Representative cationic salts include sodium, potassium, calcium, and magnesium salts and the like. See generally, *e.g.*, Berge, et al., *J. Pharm. Sci.*, 66, 1-19 (1977).

A salt of a compound of Formula (I) may be readily prepared by mixing together solutions of a compound of Formula (I) and the 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.

The term "radical" denotes a group of atoms that behaves as a single reactant in a chemical reaction, e. g., an organic radical is a group of atoms that imparts characteristic properties to a compound containing it, or which remains unchanged during a series of reactions or transformations.

The symbol " – " represents a covalent bond.

The phrase "reaction-inert solvent" or "inert solvent" refers to a solvent, or mixture of solvents, that does not interact with starting materials, reagents, intermediates or products in a manner that adversely affects their desired properties.

The terms "treat," "treating," "treated" or "treatment" as used herein includes preventative (e.g., prophylactic), palliative or curative uses or results.

The compounds of Formula (I) may contain asymmetric or chiral centers and, therefore, exist in different stereoisomeric forms. Those skilled in the art will appreciate that, unless otherwise specified, all stereoisomers (*e.g.*, enantiomers and diastereoisomers, and racemic mixtures thereof) of the novel

compounds and intermediates described, illustrated and/or discussed herein are within the scope of the claimed invention. In addition, unless otherwise specified, the present invention embraces all geometric and positional isomers. The (3S,4S) enantiomer of the core pyrrolidinyl configuration is preferred.

Diasteriomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well-known to those of ordinary skill in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diasteriomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Additional methods include resolution of racemic mixtures using chiral salts, as well as chiral chromatography.

Those skilled in the art will further recognize that the compounds of Formula (I) can exist in crystalline form as hydrates wherein molecules of water are incorporated within the crystal structure thereof and as solvates wherein molecules of a solvent are incorporated therein. All such hydrate and solvate forms are considered part of this invention.

Practitioners will appreciate that certain compounds of Formula (I) may exist as tautomeric isomers, i.e., that equilibrium exists between two isomers which are in rapid equilibrium with each other. A common example of tautomerism is keto-enol tautomerism, i.e.,



The degree to which one tautomer is present over the other depends upon various factors, including substitution pattern and solvent type. Other examples in accordance with the present invention will be recognized by those skilled in the art. All tautomeric forms of Formula (I) are included within the scope of the invention unless otherwise specified.

The present invention also includes prodrugs of the compounds of the invention. The term "prodrug" refers to a drug precursor which, following administration, releases the drug in vivo via a chemical or physiological process (e.g., upon being brought to physiological pH or through enzymatic activity). The prodrug may itself be biologically active, or may be converted to a biologically active compound (e.g. by metabolism or hydrolysis) during its residence time in the body. A discussion of the preparation and use of prodrugs is provided by Higuchi & Stella, "Prodrugs as Novel Delivery Systems", Vol.14 of the A.C.S. Symposium Series, and in "Bioreversible Carriers in Drug Design," ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. All prodrugs of the various compounds of Formula (I) are within the scope of the present invention.

The present invention also embraces isotopically-labeled compounds of Formula (I) that are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of Formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. The compounds of Formula (I), and pharmaceutically acceptable salts thereof, that contain the aforementioned isotopes and/or other isotopes of the other atoms are within the scope of the instant invention.

Certain isotopically-labeled compounds of Formula (I), for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H and ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Furthermore, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life, or reduced dosage requirements and, hence, may be preferred in some circumstances.

Isotopically-labeled compounds of Formula (I), and pharmaceutically acceptable salts thereof, can be generally prepared by carrying out analogous procedures to those disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically-labeled reagent for a non-isotopically labeled reagent.

The invention also includes pharmaceutical compositions comprising an amount of a compound of Formula (I), or a pharmaceutically acceptable salt of the compound, and optionally a pharmaceutically acceptable vehicle, carrier or diluent. In a preferred embodiment, the pharmaceutical composition is of an amount effective at inhibiting the enzyme PDE9 in a mammal. In another preferred embodiment, the mammal is a human.

The present invention includes the use of a combination of a PDE9 inhibitor compound as provided in Formula (I) and one or more additional pharmaceutically active agent(s). If a combination of active agents is administered, then they may be administered sequentially or simultaneously, in separate dosage forms or combined in a single dosage form. Accordingly, the present invention also includes pharmaceutical compositions comprising an amount of: (a) a first agent comprising a compound of Formula (I) or a pharmaceutically acceptable salt of the compound; (b) a second pharmaceutically active agent; and (c) a pharmaceutically acceptable carrier, vehicle or diluent.

Various pharmaceutically active agents may be selected for use in conjunction with the compounds of Formula (I), depending on the disease, disorder, or condition to be treated. Pharmaceutically active agents that may be used in combination with the compositions of the present invention include, without limitation:

(i) acetylcholinesterase inhibitors, such as donepezil hydrochloride (E2020, ARICEPT, MEMAC), physostigmine salicylate (ANTILIRIUM), physostigmine sulfate (ESERINE), metrifonate, neostigmine, pyridostigmine (MESTINON), ambenonium (MYTELASE), demarcarium, Debio992 (also known as ZT-1), rivastigmine (EXELON), ladostigil (also known as TV3326),

NP-0361, galantamine hydrobromide (RAZADYNE, RIMINYL, NIVALIN), tacrine (COGNEX), velnacrine maleate, memoquin, huperzine A (HUP-A), phenserine, and edrophonium (ENLON, TENSILON);

(ii) amyloid-ß (or fragments thereof), such as $A\beta_{1-15}$ conjugated to pan HLA DR-binding epitope (PADRE), ACC-001, ACI-01, ACI-24, AN-1792, Affitope AD-01, CAD106, and V-950;

(iii) antibodies to amyloid-ß (or fragments thereof), such as bapineuzumab (also known as AAB-001), AAB-002, ACI-01-Ab7, BAN-2401, intravenous Ig (GAMMAGARD), LY2062430 (humanized m266), PF-04360365 (also known as RN-1219), RN-6G, R-1450, ACU-5A5, huC091, and those disclosed in International Patent Publication Nos WO04/032868, WO05/025616, WO06/036291, WO06/069081, WO06/118959, in US Patent Publication Nos US2003/0073655, US2004/0192898, US2005/0048049, US2005/0019328, in European Patent Publication Nos EP0994728 and 1257584, and in US Patent No 5,750,349;

(iv) amyloid-lowering or –inhibiting agents (including those that reduce amyloid accumulation and fibrillization) such as bisnorcymserine (also known as BNC), pioglitazone, PBT2, flurbiprofen (ANSAID, FROBEN) and its *R*-enantiomer tarenflurbil (also known as MPC-7869; FLURIZAN), *nitroflurbiprofen*, *fenoprofen* (FENOPRON, NALFON), *ibuprofen* (ADVIL, MOTRIN, NUROFEN), ibuprofen lysinate, meclofenamic acid, meclofenamate sodium (MECLOMEN), indomethacin (INDOCIN), diclofenac sodium (VOLTAREN), diclofenac potassium, sulindac (CLINORIL), sulindac sulfide, diflunisal (DOLOBID), naproxen (NAPROSYN), naproxen sodium (ANAPROX, ALEVE), insulin-degrading enzyme (also known as insulysin), the gingko biloba extract EGb-761 (ROKAN, TEBONIN), tramiprosate (NC-758, CEREBRIL, ALZHEMED), eprodisate (NC-503, FIBRILLEX, KIACTA), compound W (3,5-bis(4-nitrophenoxy)benzoic acid), NGX-96992, neprilysin (also known as neutral endopeptidase (NEP)), scyllo-inositol (also known as scyllitol, ELND005, AZD-103), atorvastatin (LIPITOR), simvastatin (ZOCOR),

KLVFF-(EEX)3, and RAGE (receptor for advanced glycation end-products) inhibitors;

(v) alpha-adrenergic receptor agonists, such as clonidine (CATAPRES), *metaraminol* (ARAMINE), methyldopa (ALDOMET, DOPAMET, NOVOMEDOPA), tizanidine (ZANAFLEX), phenylephrine (also known as neosynephrine), methoxamine, cirazoline, guanfacine (INTUNIV), lofexidine, xylazine, modafinil (PROVIGIL), adrafinil, and armodafinil (NUVIGIL);

(vi) beta-adrenergic receptor blocking agents (beta blockers), such as carteolol, esmolol (BREVIBLOC), labetalol (NORMODYNE, TRANDATE), oxprenolol (LARACOR, TRASACOR), pindolol (VISKEN), propanolol (INDERAL), sotalol (BETAPACE, SOTALEX, SOTACOR), timolol (BLOCADREN, TIMOPTIC), acebutolol (SECTRAL, PRENT), nadolol (CORGARD), metoprolol tartrate (LOPRESSOR), metoprolol succinate (TOPROL-XL), atenolol (TENORMIN), butoxamine, and SR 59230A (Sanofi);

(vii) anticholinergics, such as amitriptyline (ELAVIL, ENDEP), butriptyline, benztropine mesylate (COGENTIN), trihexyphenidyl (ARTANE), *diphenhydramine* (BENADRYL), *orphenadrine* (NORFLEX), *hyoscyamine*, atropine (ATROPEN), scopolamine (TRANSDERM-SCOP), scopolamine methylbromide (PARMINE), dicycloverine (BENTYL, BYCLOMINE, DIBENT, DILOMINE, tolterodine (DETROL), oxybutynin (DITROPAN, LYRINEL XL, OXYTROL), penthienate bromide, propantheline (PRO-BANTHINE), cyclizine, *imipramine* hydrochloride (TOFRANIL), imipramine maleate (SURMONTIL), lofepramine, desipramine (NORPRAMIN), doxepin (SINEQUAN, ZONALON), trimipramine (SURMONTIL), and glycopyrrolate (ROBINUL);

(viii) anticonvulsants, such as carbamazepine (TEGRETOL, CARBATROL), oxcarbazepine (TRILEPTAL), phenytoin sodium (PHENYTEK), fosphenytoin (CEREBYX, PRODILANTIN), divalproex sodium (DEPAKOTE), gabapentin (NEURONTIN), pregabalin (LYRICA), topirimate (TOPAMAX), valproic acid (DEPAKENE), valproate sodium (DEPACON), 1-benzyl-5-bromouracil, progabide, beclamide, and primidone (MYSOLINE);

(ix) antipsychotics, such as lurasidone (also known as SM-13496), aripiprazole (ABILIFY), chlorpromazine (THORAZINE), haloperidol (HALDOL), flupentixol decanoate (DEPIXOL, FLUANXOL), reserpine (SERPLAN), pimozide (ORAP), fluphenazine decanoate, fluphenazine hydrochloride, prochlorperazine (COMPRO), asenapine, loxapine (LOXITANE), mesoridazine, molindone (MOBAN), perphenazine, thioridazine, thiothixine, trifluoperazine (STELAZINE), clozapine (CLOZARIL), norclozapine (ACP-104), risperidone (RISPERDAL), paliperidone (INVEGA), melperone, olanzapine (ZYPREXA), quetiapine (SEROQUEL), sertindole, sulpiride (MERESA, DOGMATYL, SULPITIL), amisulpride, ziprasidone (GEODON), blonanserin (LONASEN), and bifeprunox;

(x) calcium channel blockers such as nilvadipine (ESCOR, NIVADIL), amlodipine (NORVASC, ISTIN, AMLODIN), felodipine (PLENDIL), nicardipine (CARDENE), nifedipine (ADALAT, PROCARDIA), MEM 1003 and its parent compound nimodipine (NIMOTOP), nisoldipine (SULAR), nitrendipine, lacidipine (LACIPIL, MOTENS), lercanidipine (ZANIDIP), diltiazem (CARDIZEM), verapamil (CALAN, VERELAN), and enecadin (also known as NS-7);

(xi) catechol O-methyltransferase (COMT) inhibitors, such as tolcapone (TASMAR), entacapone (COMTAN), and tropolone;

(xii) central nervous system stimulants, such as caffeine, phenmetrazine, phendimetrazine, pemoline, fencamfamine (GLUCOENERGAN, REACTIVAN), fenethylline (CAPTAGON), pipradol (MERETRAN), deanol (also known as dimethylaminoethanol), methylphenidate (DAYTRANA), methylphenidate hydrochloride (RITALIN), dexmethylphenidate (FOCALIN), amphetamine (alone or in combination with other CNS stimulants, e.g. ADDERALL (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate)), dextroamphetamine sulfate (DEXEDRINE, DEXTROSTAT), methamphetamine (DESOXYN), lisdexamfetamine (VYVANSE), and benzphetamine (DIDREX);

(xiii) corticosteroids, such as prednisone (STERAPRED, DELTASONE), prednisolone (PRELONE), predisolone acetate (OMNIPRED, PRED MILD, PRED FORTE), prednisolone sodum phosphate (ORAPRED ODT), methylprednisolone (MEDROL); methylprednisolone acetate (DEPO-MEDROL), and methylprednisolone sodium succinate (A-METHAPRED, SOLU-MEDROL);

(xiv) dopamine receptor agonists, such as apomorphine (APOKYN), bromocriptine (PARLODEL), cabergoline (DOSTINEX), dihydrexidine, dihydroergocryptine, fenoldopam (CORLOPAM), lisuride (DOPERGIN), pergolide (PERMAX), piribedil (TRIVASTAL, TRASTAL), pramipexole (MIRAPEX), quinpirole, ropinirole (REQUIP), and rotigotine (NEUPRO);

(xv) dopamine receptor antagonists, such as tetrabenazine (NITOMAN, XENAZINE), 7-hydroxyamoxapine, droperidol (INAPSINE, DRIDOL, DROPLETAN), domperidone (MOTILIUM), L-741742, L-745870, raclopride, SCH-23390, ecopipam, SKF-83566, and metoclopramide (REGLAN);

(xvi) dopamine reuptake inhibitors such as nomifensine maleate (MERITAL), vanoxerine (also known as GBR-12909) and its decanoate ester DBL-583, and amineptine;

(xvii) gamma-amino-butyric acid (GABA) receptor agonists, such as baclofen (LIORESAL, KEMSTRO), pentobarbital (NEMBUTAL), progabide (GABRENE), and clomethiazole;

(xviii) immunomodulators such as glatiramer acetate (also known as copolymer-1; COPAXONE), MBP-8298 (synthetic myelin basic protein peptide), dimethyl fumarate, fingolimod (also known as FTY720), roquinimex (LINOMIDE), laquinimod (also known as ABR-215062 and SAIK-MS), ABT-874 (human anti-IL-12 antibody), rituximab (RITUXAN), alemtuzumab (CAMPATH), daclizumab (ZENAPAX), and natalizumab (TYSABRI);

(xix) immunosuppressants such as methotrexate (TREXALL, RHEUMATREX), mitoxantrone (NOVANTRONE), mycophenolate mofetil (CELLCEPT), mycophenolate sodium (MYFORTIC), azathioprine (AZASAN,

IMURAN), mercaptopurine (PURI-NETHOL), cyclophosphamide (NEOSAR, CYTOXAN), chlorambucil (LEUKERAN), cladribine (LEUSTATIN, MYLINAX), alpha-fetoprotein, etanercept (ENBREL), and 4-benzyloxy-5-((5-undecyl-2H-pyrrol-2-ylidene)methyl)-2,2'-bi-1H-pyrrole (also known as PNU-156804);

(xx) interferons, including interferon beta-1a (AVONEX, REBIF) and interferon beta-1b (BETASERON, BETAFERON);

(xxi) levodopa (or its methyl or ethyl ester), alone or in combination with a DOPA decarboxylase inhibitor (e.g. carbidopa (SINEMET, CARBILEV, PARCOPA, V1512), benserazide (MADOPAR), α-methyldopa, monofluromethyldopa, difluoromethyldopa, brocresine, or *m*-hydroxybenzylhydrazine);

(xxii) *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine (NAMENDA, AXURA, EBIXA), amantadine (SYMMETREL), acamprosate (CAMPRAL), besonprodil (also known as PD-196,860 or CI-1041), ketamine (KETALAR), delucemine (also known as NPS 1506), dexanabinol (also known as HU-211), dextromethorphan, dextrorphan, traxoprodil (also known as CP-101,606), himantane, idantadol (also known as V-3381), lancicemine (also known as AR-R 15896), levorphanol (DROMORAN), methadone, (DOLOPHINE), neramexane (also known as MRZ 2/579), perzinfotel, phencyclidine, tianeptine (STABLON), dizocilpine (also known as MK-801), ibogaine, voacangine, tiletamine, riluzole (RILUTEK), aptiganel (CERESTAT), gavestinel, and remacimide;

(xxiii) monoamine oxidase (MAO) inhibitors, such as selegiline (EMSAM), selegiline hydrochloride (l-deprenyl, ELDEPRYL, ZELAPAR), dimethylselegilene, brofaromine, phenelzine (NARDIL), tranylcypromine (PARNATE), moclobemide (AURORIX, MANERIX), befloxatone, safinamide (also known as PNU-151774E), isocarboxazid (MARPLAN), nialamide (NIAMID), rasageline (AZILECT), iproniazide (MARSILID, IPROZID, IPRONID), iproclozide, toloxatone (HUMORYL, PERENUM), bifemelane, desoxypeganine, harmine (also known as telepathine or banasterine),

harmaline, linezolid (ZYVOX, ZYVOXID), and pargyline (EUDATIN, SUPIRDYL);

(xxiv) muscarinic receptor (particularly M1 subtype) agonists, such as bethanechol chloride (DUVOID, URECHOLINE), pilocarpine (SALAGEN), NGX267, arecoline, L-687306, L-689660, furtrethonium iodide (FURAMON, FURANOL), furtrethonium benzensulfonate, furtrethonium *p*-toluenesulfonate, McN-A-343, oxotremorine, and carbachol (CARBASTAT, MIOSTAT, CARBOPTIC);

(xxv) nicotinic receptor agonists, such as epibatidine, ABT-089, ABT-594, AZD-0328, R-4996 (also known as MEM-63908), TC-5619, and EVP-6124;

(xxvi) neuroprotective drugs such as 2,3,4,9-tetrahydro-1*H*-carbazol-3-one oxime, AL-108, ACD3480 (also known as TC-1734), bis(4-β-D-glucopyranosyloxybenzyl)-2-β-D-glucopyranosyl-2-isobutyltartrate (also known as dactylorhin B or DHB), xaliproden (XAPRILA), dimeboline hydrochloride (DIMEBON), disufenton (NXY-059, CEROVIVE), arundic acid (ONO-2506, PROGLIA, CEREACT), citicoline (also known as cytidine 5'-diphosphocholine), edaravone (RADICUT), AEOL-10150, AGY-94806 (also known as SA-450 and Msc-1), granulocyte-colony stimulating factor (AX-200), BAY-387271 (also known as KN-387271), DP-b99, HF-0220 (17-ß-hydroxyepiandrosterone), HF-0420 (also known as oligotropin), pyridoxal 5'-phosphate (also known as MC-1), microplasmin, S-18986, piclozotan (also known as SUN-N4057), NP031112, L-seryl-L-methionyl-L-alanyl-L-lysyl-L-glutamyl-glycyl-L-valine, and SUN-N8075;

(xxvii) norepinephrine (noradrenaline) reuptake inhibitors, such as atomoxetine (STRATTERA), doxepin (APONAL, ADAPIN, SINEQUAN), nortriptyline (AVENTYL, PAMELOR, NORTRILEN), amoxapine (ASENDIN, DEMOLOX, MOXIDIL), reboxetine (EDRONAX, VESTRA), viloxazine (VIVALAN), maprotiline (DEPRILEPT, LUDIOMIL, PSYMION), bupropion (WELLBUTRIN), and radaxafine;

(xxviii) other PDE9 inhibitors, such as BAY 73-6691 and those disclosed in US Patent Publication Nos US2003/0195205, US2004/0220186, US2006/0111372, and US2006/0106035;

(xxix) other phosphodiesterase (PDE) inhibitors, including (a) PDE1 inhibitors (e.g. vinpocetine (CAVINTON, CERACTIN, INTELECTOL) and those disclosed in US Patent No 6,235,742), (b) PDE2 inhibitors (e.g. erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), BAY 60-7550, and those described in US Patent No. 6,174,884), (c) PDE4 inhibitors (e.g. rolipram, Ro 20-1724, ibudilast (KETAS), piclamilast (also known as RP73401), CDP840, cilomilast (ARIFLO), roflumilast, tofimilast, oglemilast (also known as GRC 3886), tetomilast (also known as OPC-6535), lirimifast, theophylline (UNIPHYL, THEOLAIR), arofylline (also known as LAS-31025), doxofylline, RPR-122818, or mesembrine), and (d) PDE5 inhibitors (e.g. sildenafil (VIAGRA, REVATIO), tadalafil (CIALIS), vardenafil (LEVITRA, VIVANZA), udenafil, avanafil, dipyridamole (PERSANTINE), E-4010, E-4021, E-8010, zaprinast, PF-489791, UK-357903, DA-8159, and those disclosed in International Patent Applications WO05/049616, WO06/120552, and WO07/122466);

(xxx) quinolines, such as quinine (including its hydrochloride, dihydrochloride, sulfate, bisulfate and gluconate salts), chloroquine, hydroxychloroquine (PLAQUENIL), mefloquine (LARIAM), and amodiaquine (CAMOQUIN, FLAVOQUINE);

(xxxi) β-secretase inhibitors, such as WY-25105, (+)-phenserine tartrate (POSIPHEN), LSN-2434074 (also known as LY-2434074), PNU-33312, KMI-574, SCH-745966, Ac-rER (N^2-acetyl-D-arginyl-L-arginine), loxistatin (also known as E64d), and CA074Me;

(xxxii) γ-secretase inhibitors, such as LY-411,575, LY-685,458, ELAN-G, ELAN-Z, 4-chloro-*N*-[2-ethyl-1(S)-(hydroxymethyl)butyl]benzenesulfonamide,

(xxxiii) serotonin (5-hydroxytryptamine) 1A ($5\text{-}HT_{1A}$) receptor antagonists, such as spiperone, *levo*-pindolol, BMY 7378, NAD-299, *S*(-)-UH-301, NAN 190, WAY 100635, lecozotan (also known as SRA-333);

(xxxiv) serotonin (5-hydroxytryptamine) 6 (5-HT_6) receptor antagonists, such as mianserin (TORVOL, BOLVIDON, NORVAL), methiothepin (also known as metitepine), ritanserin, ALX-1161, ALX-1175, MS-245, LY-483518 (also known as SGS518), MS-245, Ro 04-6790, RO 43-68544, Ro 63-0563, RO 65-7199, Ro 65-7674, SB-399885, SB-214111, SB-258510, SB-271046, SB-357134, SB-699929, SB-271046, SB-742457 and PRX-07034;

(xxxv) serotonin (5-HT) reuptake inhibitors such as alaproclate, citalopram (CELEXA, CIPRAMIL), escitalopram (LEXAPRO, CIPRALEX), clomipramine (ANAFRANIL), duloxetine (CYMBALTA), femoxetine (MALEXIL), fenfluramine (PONDIMIN), norfenfluramine, fluoxetine (PROZAC), fluvoxamine (LUVOX), indalpine, milnacipran (IXEL), paroxetine (PAXIL, SEROXAT), sertraline (ZOLOFT, LUSTRAL), trazodone (DESYREL, MOLIPAXIN), venlafaxine (EFFEXOR), zimelidine (NORMUD, ZELMID), bicifadine, desvenlafaxine (PRISTIQ), brasofensine, and tesofensine;

(xxxvi) trophic factors, such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF), neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF), and agents that stimulate local production of trophic factors, such as propentofylline, idebenone, and AIT-082 (NEOTROFIN);

and the like.

The invention also includes methods of inhibiting PDE9 in a mammal comprising administering to the mammal in need of such inhibition a PDE9 inhibiting amount of: (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or diluent; either alone or in combination with a second agent as described above.

The invention also includes methods of treating conditions mediated by PDE9 inhibition in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of: (a) a compound of

Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or diluent; either alone or in combination with a second agent described above.

Conditions that may be treated, controlled or prevented by the methods of the present invention include diseases and disorders associated with neurodegeneration such as: Alexander disease, Alper's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS; also known as Lou Gehrig's disease or motor neuron disease), ataxia-telangiectasia, Batten disease (also known as Spielmeyer-Vogt-Sjogren-Batten disease), Binswanger's dementia (subcortical arteriosclerotic encephalopathy), bipolar disorders, bovine spongiform encephalopathy (BSE), Canavan disease, chemotherapy-induced dementia, Cockayne syndrome, corticobasal degeneration, Creutzfeldt-Jakob disease, depression, Down syndrome, frontotemporal lobar degeneration (including frontotemporal dementia, semantic dementia, and progressive nonfluent aphasia), Gerstmann-Straüssler-Scheinker disease, glaucoma, Huntington's disease (chorea), HIV-associated dementia, hyperkinesias, Kennedy's disease, Korsakoff's syndrome (amnesic-confabulatory syndrome), Krabbe's disease, Lewy body dementia, logopenic progressive aphasia, Machado-Joseph disease (spinocerebellar ataxia type 3), multiple sclerosis, multiple system atrophy (olivopontocerebellar atrophy), myasthenia gravis, Parkinson's disease, Pelizaeus-Merzbacher disease, Pick's disease, pre-senile dementia (mild cognitive impairment), primary lateral sclerosis, primary progressive aphasia, radiation-induced dementia, Refsum's disease (phytanic acid storage disease), Sandhoff disease, Schilder's disease, schizophrenia, semantic dementia, senile dementia, Shy-Drager syndrome, spinocerebellar ataxias, spinal muscular atrophies, Steele-Richardson-Olszewski disease (progressive supranuclear palsy), tabes dorsalis, tardive dyskinesia, vascular amyloidosis, and vascular dementia (multi-infarct dementia).

Preferably the neurodegenerative disease or disorder is Alzheimer's disease.

Other conditions and disorders associated with PDE9 that may be treated or controlled by the methods of the present invention include disorders of the urogenital system such as sexual dysfunction, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), diabetes, cardiovascular disorders or diseases such as systemic hypertension, pulmonary hypertension, congestive heart failure, coronary artery disease, atherosclerosis, stroke, thrombosis, conditions of reduced blood vessel patency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease, renal disease, angina (including stable, unstable, and variant (Prinzmetal) angina), and any condition where improved blood flow leads to improved end organ function.

The present invention also relates to methods for promoting neurorestoration and functional recovery in patients suffering from traumatic or non-traumatic injury to the brain, spinal cord or peripheral nerves. Traumatic brain injuries include both closed head injuries (in which the skull is not broken) and open, or penetrating, head injuries (in which an object pierces the skull and breaches the dura mater), wherein sudden trauma (e.g., accidents, falls, assaults) causes damage to the brain tissue by tearing, stretching, bruising, or swelling. Causes of non-traumatic brain injuries include aneurism, stroke, meningitis, oxygen deprivation due to anoxia, hypoxia, or ischemia, brain tumor, infection (e.g. encephalitis), poisoning, substance abuse, and the like. The present invention is useful for the treatment of cognitive impairment and cognitive dysfunction resulting from brain injuries as well as from neurodegenerative diseases and disorders.

The present invention also relates to methods for preventing the above-described conditions in a mammal, including human, comprising the steps of administering to the mammal an amount of: (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof; or (b) a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically

acceptable salt thereof, in a pharmaceutically acceptable vehicle, carrier or diluent; either alone or in combination with a second agent as described above, as part of an appropriate dosage regimen designed to prevent said condition.

The present invention also relates to methods for improving cognitive deficits, including deficits in perception, concentration, learning, memory, communication, reasoning, and problem-solving.

The appropriate dosage regimen, the amount of each dose administered and the intervals between doses of the compound will depend, among others, upon the compound of Formula (I) of this invention being used, the type of pharmaceutical compositions being used, the characteristics of the subject being treated and the type and severity of the conditions to be treated. In general, an effective dose for compounds of Formula (I) or pharmaceutically acceptable salts thereof, is in the range of from about 0.1 mg to about 3,500 mg per day. For a normal adult human having a body mass of about 70 kg, a dosage in the range of from about 0.01 mg to about 50 mg per kg body mass is typically sufficient, and preferably from about 0.2 to 2.5 mg per kg, in single or divided doses daily. Administration may be in single (*e.g.*, once daily) or multiple doses or via constant infusion.

Some variability in the general dosage range may be required depending upon the age and mass of the subject being treated, the intended route of administration, the particular compound being administered, and the like. The determination of dosage ranges and optimal dosages for a particular mammalian subject is within the ability of a skilled person having benefit of the instant disclosure.

The compounds of Formula (I) may be administered by a variety of conventional routes of administration, including oral, buccal, sublingual, ocular, topical (e.g., transdermal), parenteral (e.g., intravenous, intramuscular, or subcutaneous), rectal, intracisternal, intravaginal, intraperitoneal, intravesical, local (e.g., powder, ointment, or drop), nasal and/or inhalation dosage forms or using a "flash" formulation, *i.e.*, allowing the medication to

dissolve in the mouth without the need to use water. As will be recognized by one of skill in the art, the appropriate dosage regimen, the amount of each dose administered and the intervals between doses of the compound will depend upon the compound of Formula (I), or the prodrug thereof, being used, the type of pharmaceutical compositions being used, the characteristics of the subject being treated, and/or the severity of the conditions being treated.

Methods of preparing various pharmaceutical compositions with amounts of active ingredients are known, or will be apparent in light of this disclosure, to those skilled in this art. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th Ed. (1995).

Suitable pharmaceutical carriers, vehicles and diluents for such compositions include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining a compound of this invention and pharmaceutically acceptable carriers, vehicles or diluents are readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert conventional pharmaceutical excipient (or carrier) such as sodium citrate, calcium carbonate, or dicalcium phosphate, or (a) fillers or extenders, such as for example, starches, lactose, sucrose, mannitol and silicic acid; (b) binders, such as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c) humectants, such as for example, glycerol; (d) disintegrating agents, such as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, such as for example, paraffin; (f) absorption accelerators, such as for example, quaternary ammonium compounds; (g) wetting agents, such as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents,

such as for example, kaolin and bentonite; and/or (i) lubricants, such as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate or mixtures thereof. In the case of capsules and tablets, the dosage forms may further comprise buffering agents.

Solid dosage forms may be formulated as modified release and pulsatile release dosage forms containing excipients such as those detailed above for immediate release dosage forms together with additional excipients that act as release rate modifiers, these being coated on and/or included in the body of the device. Release rate modifiers include, but are not limited to, hydroxypropylmethyl cellulose, methyl cellulose, sodium carboxymethylcellulose, ethyl cellulose, cellulose acetate, polyethylene oxide, xanthan gum, ammoniomethacrylate copolymer, hydrogenated castor oil, carnauba wax, paraffin wax, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, methacrylic acid copolymer and mixtures thereof. Modified release and pulsatile release dosage forms may contain one or a combination of release rate modifying excipients.

The pharmaceutical compositions of the invention may further comprise fast dispersing or dissolving dosage formulations (FDDFs). The terms dispersing or dissolving as used herein to describe FDDFs are dependent upon the solubility of the drug substance used i.e., where the drug substance is insoluble, a fast dispersing dosage form may be prepared, and where the drug substance is soluble, a fast dissolving dosage form may be prepared.

Solid compositions of a similar type may also be employed as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known to one of ordinary skill in the art. They may also comprise opacifying agents, and can also be of such composition that they release the active compound(s) in a delayed, sustained or controlled manner. Examples

of embedding compositions that can be employed are polymeric substances and waxes. The active compound(s) can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage form may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethanol, isopropanol, ethyl carbonate, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame seed oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances, and the like.

In addition to the active compound(s), the pharmaceutical composition may further include suspending agents, such as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, or mixtures of these substances, and the like. Sweeteners, flavoring, and perfuming agents may also be included.

The pharmaceutical compositions of the invention may further comprise adjuvants, such as preserving, wetting, emulsifying and dispersing agents. Prevention of microorganism contamination of the instant compositions can be accomplished with various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of injectable pharmaceutical compositions may be affected by the use of agents capable of delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration, solutions in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solutions may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These

aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

For intranasal administration or administration by inhalation, the compounds of Formula (I) are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of a compound of this invention. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound or compounds of the invention and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention may also be configured for treatments in veterinary use, where a compound of the present invention, or a veterinarily acceptable salt thereof, or veterinarily acceptable solvate or pro-drug thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary practitioner will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

In general, the compounds of Formula (I), and pharmaceutically acceptable salts thereof, may be prepared according to the exemplary routes disclosed in the Schemes and Examples below, as well as by other conventional preparative procedures known, or apparent in light of the instant disclosure, to one of ordinary skill in the art. These processes form further aspects of the invention.

Some of the starting compounds for the reactions described in the Schemes and Examples are prepared as illustrated herein. All other starting compounds may be obtained from general commercial sources, such as Sigma-Aldrich Corporation, St. Louis, MO.

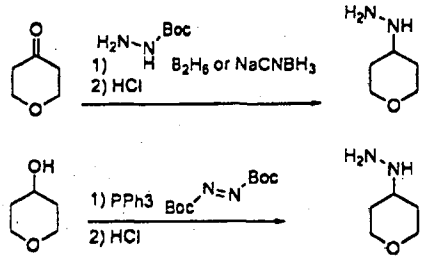
Unless indicated otherwise, the following experimental abbreviations have the indicated meanings:

μL – microliter	m – multiplet
bd – broad doublet	MHz – megahertz
bm – broad multiplet	Min(s) – minute(s)
BOC – *t*-butoxycarbonyl	MeOH – methanol
bs – broad singlet	Mg – milligram
$CDCl_3$ – deuterated chloroform	ml – milliliter
CD_3OD – deuterated methanol	mmol – millimoles
dd – doublet of doublets	MPLC – medium pressure liquid chromatography
DMF – dimethylformamide	MS – mass spectroscopy
DMSO – dimethyl sulfoxide	NMR – nuclear magnetic resonance
dt – doublet of triplets	ppm – parts per million
EtOAc – ethyl acetate	psi – pounds per square inch
EtOH – ethanol	s – singlet
h (e.g., 1h, 2h) – hour(s)	SPA – scintillation proximity assay
H (e.g., 1H, 2H) – hydrogen(s)	t – triplet
Hz – hertz	THF – tetrahydrofuran
IPA – isopropyl alcohol	Tris – tris(hydroxymethyl)aminomethane
J – spin-spin coupling constant	
LC – liquid chromatography	

The methods disclosed in the instant Schemes and Examples are intended for purposes of exemplifying the instant invention only and are not to be construed as limitations thereon.

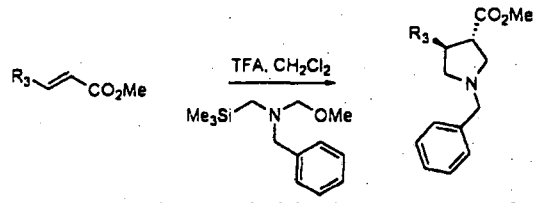
Scheme 1 exemplifies multiple ways to form aliphatic hydrazines that can utilized to prepare compounds in this patent. Ketones can be converted to the hydrazide imine and reduced with borane or sodium cyanoborohydride. Other reducing agents can also be utilized. The boc group can then be removed with acid to form the desired hydrazine intermediate. Alternatively aliphatic alcohols can be converted to boc-protected hydrazines by treatment with triphenyl phosphine and di-*t*-butyl diazacarboxylate. The boc groups can again be removed with acid to liberate the hydrazine. Aromatic hydrazine synthesis is well known in the literature by converting anilines to hydrazines through diazotization chemistry followed by reduction.

Scheme 1



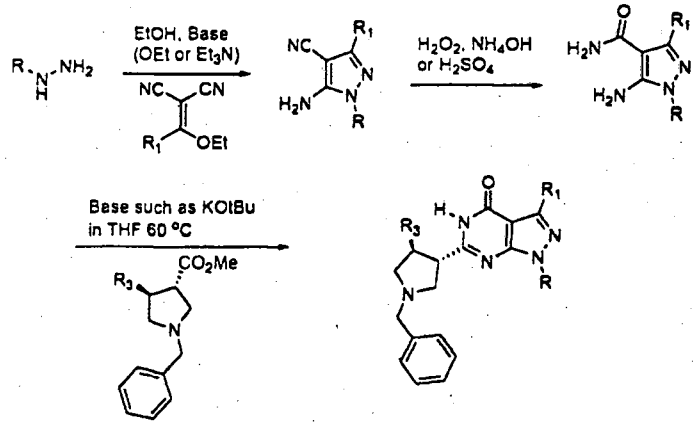
The pyrrolidine intermediates can be formed by coupling alpha-beta unsaturated esters with N-(methoxymethyl)(phenyl)-N-((trimethylsilyl)methyl)methanamine which is commercially available by catalysis with acid. This chemistry is exemplified in the experimental section below and also by numerous literature examples such as Hosomi et al., *Chem. Lett.* 13(7) 1117-1120, 1984. The pyrrolidines have also been synthesized in an enantiomeric pure fashion by either employing chiral auxiliaries on the ester (see Nichols et al., *Org. Lett.*, 8(7), 1495-1498, 2006) or by utilizing a chiral benzyl amine in the cycloaddition chemistry (see Haight et al., *Org. Proc. Res. Dev.*, 8(6), 897-902, 2004).

Scheme 2



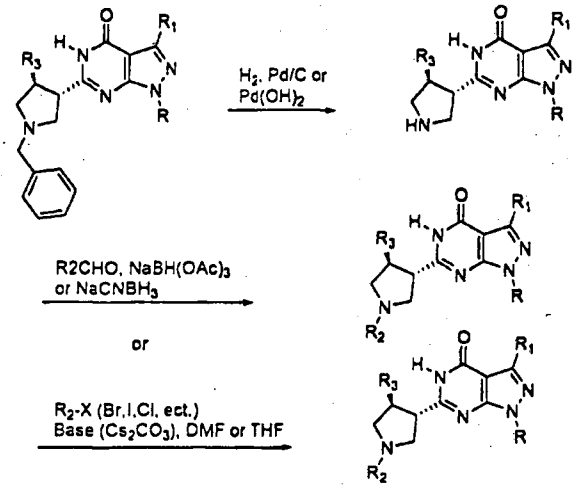
Hydrazines can then be coupled in the presence of a base such as sodium methoxide or triethylamine with 2-(ethoxymethylene)malononitrile or substituted variants to afford the desired amino cyano pyrazoles. The cyano group can be oxidized by a variety of reagent but two conditions have been utilized to prepare compounds for this patent. Concentrated sulfuric acid or hydrogen peroxide with ammonium hydroxide has afforded the amino-amide-pyrazoles. The amino-amide pyrazoles can then be coupled with esters in the presence of a base such as potassium t-butoxide with heated. The solvent of choice for this reaction has been tetrahydrofuran and in some cases dehydrating agents such as molecular sieves can be employed to improve upon the yields of the coupling.

Scheme 3



The benzyl group can then be removed via standard hydrogenation conditions to provide the secondary amine that is ready for further functionalization. The amine can be alkylated with alkyl halides in the presence of base or reductive amination chemistry utilizing a variety of hydride reducing agents can provide the desired compounds.

Scheme 4

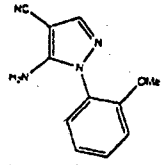


EXAMPLES

The Examples below are intended to illustrate particular embodiments of the invention and preparations thereto and are not intended to limit the specification, including the claims, in any manner. Unless otherwise noted, all reagents employed were obtained commercially.

EXAMPLE 1

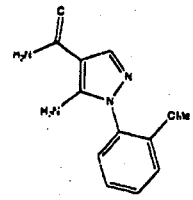
(a) 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile



To a solution of 1-(2-methoxyphenyl)hydrazine hydrogen chloride (3g, 0.017 mol) in ethanol (50 mL) was added 2-(methoxymethylene)malononitrile (1.89 g, 0.9 eq.) and sodium methoxide (1.92g, 2.1 eq). The reaction mixture was heated at reflux for 18h and concentrated. The reaction mixture was partitioned between brine and ethyl acetate. The organic layer was separated, dried with magnesium sulfate, filtered and concentrated. MPLC Biotage chromatography eluting with 20-60% ethyl acetate/hexanes afforded the title compound in 53% yield (1.9g). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.64 (m,

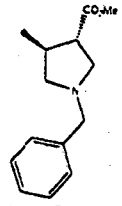
1 H), 7.40 (m, 2H), 7.08 (m,2H), 4.51 (bs, 2H), 3.87 (s, 3 H); MS: (M⁺H m/z = 215.2).

(b) 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide



To a solution of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile (1.53g) in saturated ammonium hydroxide (30 mL) was added 30% hydrogen peroxide solution (6 mL). The reaction stirred for 18h at ambient temperature and was slowly quenched with 60 mL of a saturated sodium sulfate solution. The aqueous layer was extracted with ethyl acetate, dried with magnesium sulfate, filtered and concentrated. MPLC Biotage chromatography eluting with 2-6% methanol/methylene chloride provided the title compound 1.38g (84%). 400 MHz ^{1}H NMR (DMSO) δ 7.79 (s, 1 H), 7.42 (m, 1H), 7.25 (d, *J*=7.5 Hz, 2H), 7.19 (d, *J*=8.3 Hz, 2 H), 7.03 (t, J=6.2 Hz, 1H), 5.83 (s,2H), 3.76 (s, 3 H); MS: (M⁺H *m/z* = 233.2).

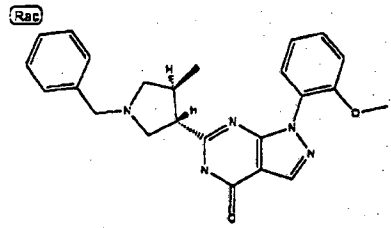
(c) (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate



To a solution of (E)-methyl but-2-enoate (1.6 g) was added toluene (30 mL), N-(methoxymethyl) (phenyl)-N-((trimethylsilyl)methyl)methanamine (3.7g) and trifluoroacetic acide (1.5g). The reaction mixture was heated at 50°C for 18h. The reaction mixture was concentrated, quenched with saturated sodium bicarbonate, extracted with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via MPLC chromatography eluting with 20-30% ethyl acetate/hexanes provided the title compound (1.5g). 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.20 (m, 5H), 4.15-4.08

(m, 1H), 3.66-3.53 (m, 2H), 2.87-2.74 (m, 2H), 2.53-2.44 (m, 2H), 2.23-2.19 (m, 1H), 1.23 (t, *J* =7.1 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H).

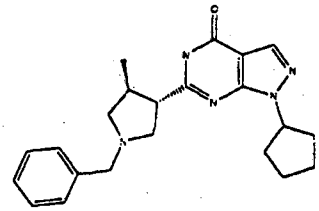
(d) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (241 mg) and 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide (200mg) was added a solution of potassium t-butoxide in (1M) in THF (4.31 mL, 5 eq.) The reaction mixture was heated at reflux for 16h and poured into saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, dried with magnesium sulfate, filtered and concentrated. MPLC Biotage chromatography eluting with 1-4% methanol/methylene chloride with 0.5% saturated ammonium hydroxide provided 79mg of the title compound. 400 MHz ^{1}H NMR (DMSO) δ 8.16 (d, *J*=7.9 Hz, 1H), 7.92 (s, 1 H), 7.34 (m, 5H), 7.09 (m, 1H), 6.92 (m, 2H), 3.89 (s, 3H), 3.84 (m, 1H), 3.71 (m, 1H), 3.37 (t, J=9.1 Hz, 1H), 3.09 (m, 1H), 2.85 (m, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.03 (m, 2H), 1.19 (d, *J*=7.1 Hz, 3H); MS: (M^+H m/z = 416.1).

EXAMPLE 2

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

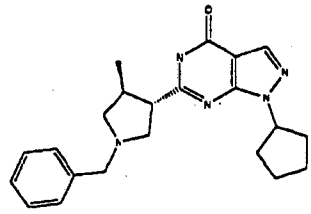


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-

carboxamide provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.00 (s, 1H), 7.38-7.23 (m, 5H), 5.14-5.10 (m, 1H), 3.80-3.57 (m, 2H), 3.34 (t, *J* = 8.3 Hz, 1H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.80-2.78 (m, 1H), 2.53-2.49 (m, 1H), 2.41-2.38 (m, 1H), 2.10-1.89 (m, 7H), 1.70-1.66 (m, 2H), 1.17 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 378.1).

EXAMPLE 3

6-[(3S,4S)1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

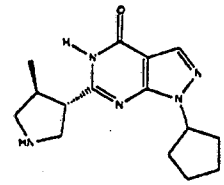


The racemate was separated on Chiralcel OD chiral HPLC column, Mobile Phase 90/10 Heptane/EtOH, T_R = 6.807, to provide the enantiomer. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.38-7.22 (m, 5H), 5.27-5.10 (m, 1H), 3.78 (d, *J*= 12.5 Hz, 1H), 3.6 (d, *J*= 12.5 Hz, 1H), 3.34 (t, *J*= 8.3 Hz, 1H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.80-2.78 (m, 1H), 2.52-2.48 (m, 1H), 2.41-2.38 (m, 1H), 2.10-1.89 (m, 7H), 1.70-1.66 (m, 2H), 1.18(d, *J*= 6.6 Hz, 3H). MS: (M^+H m/z = 378.1).

Chiralcel OD, Mobile Phase 90/10 Heptane/IPA, T_R = 9.433.

EXAMPLE 4

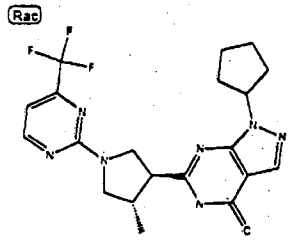
(a) 1-cyclopentyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



A solution of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (970mg) in ethanol 25 mL was added to a Parr bottle. Acetic acid (2.5 mL) and Pd(OH)2 (500

mg) was added. The reaction mixture was placed on a hydrogenator under 40 PSI for 16h. The reaction mixture was filtered through Celite and concentrated. The reaction mixture was partitioned between saturated bicarbonate solution and methylene chloride. The layers were separated and the aqueous layer was extracted 6x with methylene chloride. The organic layer was dried with magnesium sulfate, filtered and concentrated to provide 429 mg of the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 9.25 (brs, 1H), 8.02 (s, 1H), 5.20-5.17 (m, 1H), 3.91 (m, 1H), 3.77-3.68 (m, 2H), 3.46-3.44 (m, 1H), 3.10 (m, 1H), 2.89 (m, 1H), 2.13-1.87 (m, 6H), 1.74-1.65 (m, 2H), 1.20 (d, J = 6.2 Hz, 3H). MS: (M^+H m/z = 288.1).

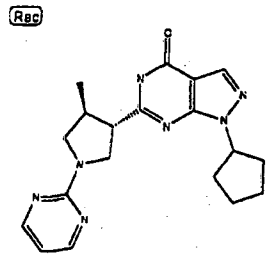
(b) 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-[4-(trifluoromethyl)pyrimidin-2-yl]pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 1-cyclopentyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (40mg) in dimethylformamide (1ml) was added cesium carbonate (2eq.) and 2-chloro-4-(trifluoromethyl)pyrimidine (1.2 eq.) and the reaction mixture was heated at 60 °C for 90 min. The reaction mixture was poured into saturated sodium bicarbonate, extracted with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via MPLC Biotage chromatography eluting with 20-60% ethyl acetate/hexanes provided 40 mg of the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.51 (d, J = 5.0 Hz, 1H), 8.02 (m, 1H), 6.79 (d, J = 4.6 Hz, 1H), 5.16-5.08 (m, 1H), 4.243.97 (m, 3H), 3.37-3.32 (m, 1H), 3.20-3.14 (m, 1H), 2.09-2.05 (m, 3H), 1.96-1.90 (m, 1H), 1.73-1.56 (m, 5H), 1.24 (d, J = 6.6 Hz, 3H). MS: (M^+H m/z = 434.1).

EXAMPLE 5

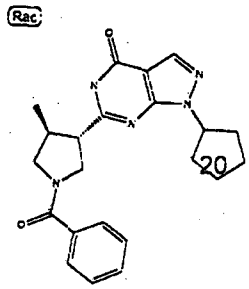
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-pyrimidin-2-ylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(trifluoromethyl)pyrimidin-2-yl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 2-chloropyrimidine provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.29 (d, J = 5.0 Hz, 2H), 7.96 (s, 1H), 6.60 (t, J = 5.0 Hz, 1H), 5.08-5.04 (m, 1H), 4.06-3.87 (m, 3H), 3.23-3.18 (m, 1H), 3.12 (q, J = 7.9 Hz, 1H), 2.80-2.76 (m, 1H), 2.05-1.98 (m, 4H), 1.90-1.82 (m, 2H), 1.66-1.61 (m, 2H), 1.17 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 366.1).

EXAMPLE 6

6-[(3,4-trans)-1-benzoyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

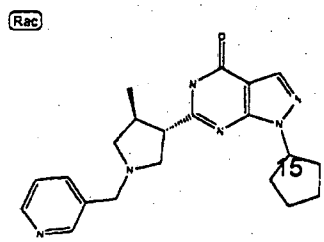


To a solution of 1-cyclopentyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (40 mg) in methylene chloride (1 ml) was added triethyl amine (2.5 eq.) and benzoyl chloride (1.2 eq.) and the reaction mixture was stirred at ambient temperature for 1h. The reaction mixture was poured into saturated sodium bicarbonate, extracted with methylene chloride,

dried with magnesium sulfate, filtered and concentrated. Biotage MPLC chromatography eluting with 2-4% methanol/methylene chloride provided the title compound (27mg). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.06-8.03 (m, 1H), 7.57-7.50 (m, 2H), 7.43-7.37 (m, 3H), 5.20-5.13 (m, 1H), 4.16-4.03 (m, 1H), 3.92 (d, *J* = 8.3 Hz, 1H), 3.81-3.76 (m, 1H), 3.47-3.29 (m, 1H), 3.17-3.03 (m, 1H), 2.84-2.67 (m, 1H), 2.11-1.80 (m, 3H), 1.79-1.72 (m, 1H), 1.56-1.30 (m, 4H), 1.21-1.11 (m, 3H). MS: (M^+H m/z = 392.1).

EXAMPLE 7

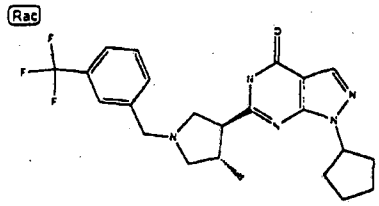
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 1-cyclopentyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (40 mg) in 1,2-dichloroethane (2 mL) was added acetic acid (2 eq.), nicotinaldehyde (1.5 eq.) and sodium triacetoxy borohydride (58 mg). The reaction mixture was heated at 40 °C for 4h, poured into saturated sodium bicarbonate, extracted with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via Biotage MPLC chromatography eluting with 1-4% methanol/methylene chloride/0.5% ammonium hydroxide provided the title compound (47 mg). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.55 (m, 2H), 2.02 (s, 1H), 7.84 (m, 1H), 7.36 (m, 1H), 5.16-5.09 (m, 1H), 3.82-3.60 (m, 2H), 3.36 (m, 1H), 3.05-2.38 (m, 4H), 2.13-1.89 (m, 7H), 1.73-1.68 (m, 2H), 1.21 (m, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 379.1).

EXAMPLE 8

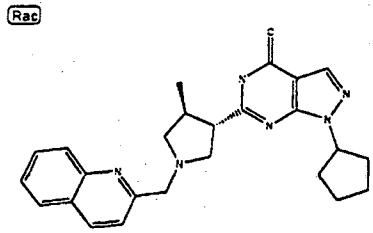
1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[3-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 3-(trifluoromethyl)benzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.66 (s, 1H), 7.53-7.50 (m, 3H), 5.16-5.09 (m, 1H), 3.80 (m, 1H), 3.69-3.66 (m, 1H), 3.35 (m, 1H), 2.99 (m, 1H), 2.83 (m, 1H), 2.42 (m, 1H), 2.12-1.93 (m, 7H), 1.74-1.68 (m, 2H), 1.56 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 446.0).

EXAMPLE 9

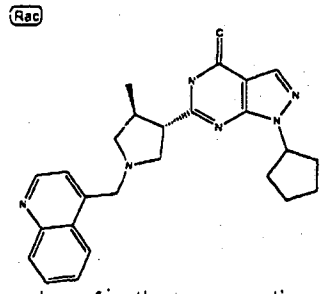
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.22-8.15 (m, 2H), 8.07 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 8.3 Hz, 1H), 7.69-7.50 (m, 2H), 5.18-5.11 (m, 1H), 4.25 (m, 1H), 3.91 (m, 1H), 3.71 (m, 1H), 3.49 (m, 1H), 3.17 (m, 1H), 2.87 (m, 1H), 2.73-2.45 (m, 2H), 2.13-1.94 (m, 6H), 1.75-1.68 (m, 2H), 1.23 (d, *J* = 7.1Hz, 3H). MS: (M^+H m/z = 429.1).

EXAMPLE 10

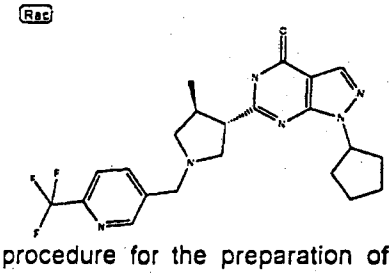
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.92-8.89 (m, 1H), 8.27-8.25 (m, 1H), 8.18-8.16 (m, 1H), 8.00 (s, 1H), 7.80-7.74 (m, 2H), 7.63-7.50 (m, 1H), 5.14-5.07 (m, 1H), 4.18 (m, 2H), 3.37 (m, 1H), 3.10-2.30 (m, 5H), 2.15-1.93 (m, 6H), 1.74-1.64 (m, 2H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 429.1).

EXAMPLE 11

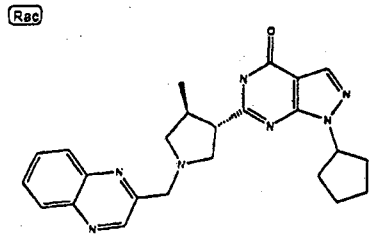
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-(trifluoromethyl)nicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.63 (m, 1H), 8.01 (s, 1H), 7.7 (d, *J*= 7.80 Hz, 1H), 5.12 (m, 1H), 4.82 (m, 1H), 3.79 (q, *J*=13.2, 16.2, Hz, 2H), 3.32 (t, *J*=8.5 Hz, 1H), 3.02 (m, 1H), 2.86 (m, 1H), 2.63 (m, 1H), 2.45 (m, 1H), 2.12-2.88 (m, 6H),), 1.74-1.64 (m, 3H), 1.32 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 447.0).

EXAMPLE 12

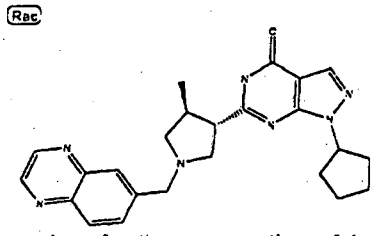
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoxaline-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.31-8.29 (m, 1H), 8.05 - 8.08 (m, 2H), 7.79-7.70 (m, 2H), 5.16-5.12 (m, 1H), 4.32-4.28 (m, 1H), 3.94-3.98 (m, 1H), 3.46 (t, *J* = 8.3 Hz, 1H), 3.26 (d, *J* = 9.5 Hz, 1H), 2.90-2.88 (m, 1H), 2.64-2.60 (m, 1H), 2.50-2.47 (m, 1H), 2.18 (t, *J* = 8.3 Hz, 1H), 2.11-1.91 (m, 6H), 1.71-1.66 (m, 2H), 1.23 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 430.1).

EXAMPLE 13

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

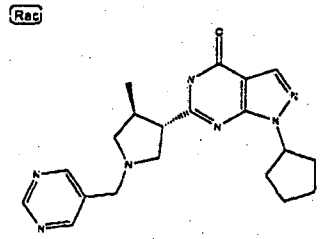


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoxaline-6-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.07-7.93 (m, 3H), 5.15-5.08 (m, 1H), 4.00-3.87 (m, 2H), 3.37 (t, *J* = 8.7 Hz, 1H), 3.04 (d, *J* = 9.5 Hz, 1H), 2.85-2.84 (m, 1H), 2.66-

2.62 (m, 1H), 2.46-2.42 (m, 1H), 2.11-1.92 (m, 7H), 1.71-1.63 (m, 2H), 1.20 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 430.1).

EXAMPLE 14

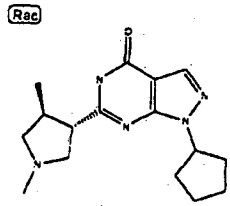
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyrimidin-5-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting pyrimidine-5-carbaldehyde provided the title compound. 400 MHz ^1H NMR, ($CDCl_3$) δ 9.16 (s, 1H), 8.76 (s, 2H), 8.02 (s, 1H), 5.17-5.10 (m, 1H), 3.78-3.69 (m, 2H), 3.27 (t, *J* = 8.7 Hz, 1H), 3.07 (d, *J* = 9.5 Hz, 1H), 2.89 (m, 1H), 2.69 (m, 1H), 2.48-2.46 (m, 1H), 2.12-1.89 (m, 6H), 1.74-1.63 (m, 3H), 1.26-1.19 (m, 3H). MS: (M^+H m/z = 380.1).

EXAMPLE 15

1-cyclopentyl-6-[(3,4-trans)-1,4-dimethylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

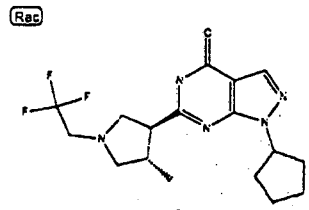


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting formaldehyde provided the title compound. 400 MHz ^1H NMR, ($CDCl_3$) δ 8.04 (s, 1H), 5.18-5.11 (m, 1H), 3.39 (m, 1H), 3.15 (m, 1H), 3.03-2.96 (m, 1H), 2.70 (m, 1H), 2.51 (m, 4H),

2.15-1.90 (m, 7H), 1.75-1.66 (m, 2H), 1.20 (d, J = 6.6 Hz, 3H). MS: (M^+H m/z = 302.2).

EXAMPLE 16

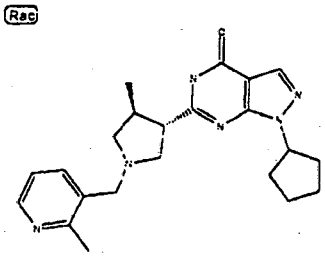
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 1-cyclopentyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (40 mg) in dimethyl formamide (1.5mL) was added sodium carbonate (30 mg) and 1,1,1-trifluoro-2-iodoethane (1.1 eq.). The reaction mixture was heated at 40 °C for 3 days. An additional 3 eq. of 1,1,1-trifluoro-2-iodoethane along with cesium carbonate (2eq.) and the reaction mixture was heated at 60 °C for 3 days. The reaction mixture was poured into saturated sodium bicarbonate, extracted with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via MPLC Biotage eluting with 0.5-2% methanol/methylene chloride/0.5% ammonium hydroxide provided the title compound (9mg). 400 MHz ^{1}H NMR, ($CDCl_3$) δ 8.03 (s, 1H), 5.16-5.10 (m, 1H), 3.50-3.48 (m, 1H), 3.30-3.25 (m, 2H), 2.52 (m, 1H), 2.25 (m, 1H), 2.13-1.94 (m, 5H), 1.72-1.57 (m, 6H), 1.22 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 370.1).

EXAMPLE 17

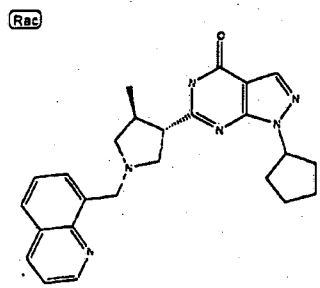
1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 2-methylnicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.40-8.39 (m, 1H), 7.99 (s, 1H), 7.62-7.60 (m, 1H), 7.12-7.09 (m, 1H), 5.15-5.08 (m, 1H), 3.73-3.65 (m, 2H), 3.30 (t, *J* = 8.7 Hz, 1H), 3.04 (d, *J* = 9.95 Hz, 1H), 2.86-2.84 (m, 1H), 2.66-2.62 (m, 4H), 2.46-2.39 (m, 1H), 2.11-1.89 (m, 7H), 1.71-1.64 (m, 2H), 1.19 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 393.2).

EXAMPLE 18

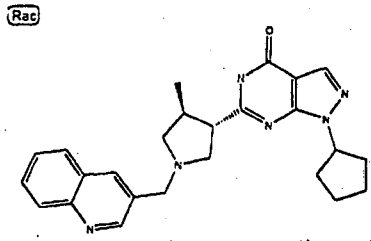
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-8-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 9.10-9.09 (m, 1H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.98 (s, 1H), 7.76-7.74 (d, *J*= 7.88 Hz, 2H), 7.50 (t, *J*= 7.88 Hz, 1H), 7.45-7.42 (m, 1H), 5.14-5.07 (m, 1H), 4.52 (d, *J*= 12.40 Hz, 1H), 4.21 (d, *J*= 12.40 Hz, 1H), 3.34 (t, *J* = 8.3 Hz, 1H), 3.1 (d, *J* = 9.95 Hz, 1H), 2.8-2.79 (m, 1H), 2.71-2.67 (m, 1H), 2.37-2.31 (m, 1H), 2.10-1.88 (m, 7H), 1.72-1.62 (m, 2H), 1.17 (d, *J*= 6.64 Hz, 3H). MS: (M^+H m/z = 429.2).

EXAMPLE 19

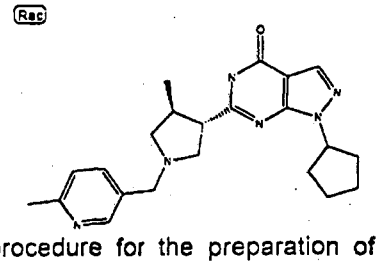
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.87 (s, 1H), 8.29 (s, 1H), 8.07 (d, *J*= 7.8 Hz, 1H), 8.02 (s, 1H), 7.89 (d, *J*= 7.9 Hz, 1H), 7.70-7.66 (m, 1H), 7.54 (t, *J*= 7.5 Hz, 1H), 5.16-5.08 (m, 1H), 4.02-3.98 (m, 1H), 3.86-3.83 (m, 1H), 3.47 (s, 1H), 3.40 (t, *J*= 8.3 Hz, 1H), 3.07 (d, *J* = 8.5 Hz, 1H), 2.85 (m, 1H), 2.65-2.61 (m, 1H), 2.47-2.46 (m, 1H), 2.15-1.87 (m, 6H), 1.73-1.63 (m, 2H), 1.20 (d, *J*= 7.1 Hz, 3H). MS: (M$^+$H m/z = 429.2).

EXAMPLE 20

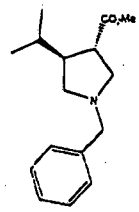
1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(6-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-methylnicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.37 (d, *J*= 1.2 Hz, 1H), 8.00 (s, 1H), 7.73 (dd, *J*= 7.9, 2.1 Hz, 1H), 7.18 (d, *J*= 8.3 Hz, 1H), 5.16-5.08 (m, 1H), 3.76-3.72 (m, 1H), 3.61-3.57 (m, 1H), 3.32 (t, *J*= 8.71 Hz, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.83-2.81 (m, 1H), 2.57-2.51 (m, 4H), 2.42-2.38 (m, 1H), 2.11-1.89 (m, 7H), 1.72-1.64 (m, 2H), 1.19 (d, *J*= 7.1 Hz, 3H). MS: (M$^+$H m/z = 393.2).

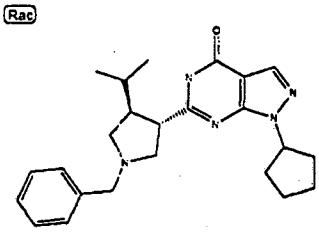
EXAMPLE 21

(a) (3,4-trans)-methyl 1-benzyl-4-isopropylpyrrolidine-3-carboxylate



Following the procedure for the preparation of (3,4-trans)-methyl 1-benzyl-4-methyl pyrrolidine-3-carboxylate but substituting (E)-methyl 4-methylpent-2-enoate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.31-7.20 (m, 5H), 3.66 (s, 3H), 3.62-3.49 (m, 2H), 2.79-2.69 (m, 3H), 2.31-2.27 (m, 2H), 1.61-1.56 (m, 1H), 1.27-4.25 (m, 1H), 0.86 (t, *J* =2.9 Hz, 6H). MS: (M^+H m/z = 262.2).

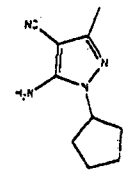
(b) 6-[(3,4-trans)-1-benzyl-4-isopropylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and (3,4-trans)-methyl 1-benzyl-4-isopropylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.38-7.32 (m, 4H), 7.27-7.24 (m, 1H), 5.13-5.05 (m, 1H), 3.78 (d, *J*= 12.5 Hz, 1H), 3.6 (d, *J*= 12.5 Hz, 1H), 3.27-3.21 (m, 1H), 2.98-2.96 (m, 2H), 2.37 (m, 1H), 2.10-1.88 (m, 7H), 1.69-1.60 (m, 3H), 0.98 (d, *J*= 6.6 Hz, 3H), 0.86 (d, *J*= 6.6 Hz, 3H). MS: (M^+H m/z = 406.1).

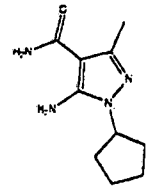
EXAMPLE 22

(a) 5-amino-1-cyclopentyl-3-methyl-1H-pyrazole-4-carbonitrile



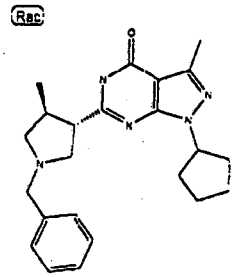
Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-cyclopentylhydrazine and 2-(1-methoxyethylidene)malononitrile provided the title compound. ^{1}H NMR (300 MHz, CDCl3): δ 4.24 (m, 3H), 2.24 (s, 3H), 2.01 (m, 4H), 1.90 (m, 2H), 1.67 (m, 2H).

(b) 5-amino-1-cyclopentyl-3-methyl-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-cyclopentyl-3-methyl-1H-pyrazole-4-carbonitrile provided the title compound. ^{1}H NMR (300 MHz, CDCl3): δ 5.39 (br, 2H), 5.32 (br, 2H), 4.26 (m, 1H), 2.38 (s, 3H), 2.04 (m, 4H), 1.9 (m, 2H), 1.66 (m, 2H).

(c) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-3-methyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

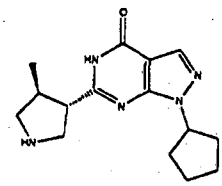


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-3-methyl-1H-

pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.45-7.20 (m, 5H), 5.13-4.96 (m, 1H), 3.85-3.61 (m, 2H), 3.45-3.30 (m, 1H), 3.08-2.98 (m, 1H), 2.82-2.74 (m, 1H), 2.60-2.45 (m, 4H), 2.45-2.30 (m, 1H), 2.18-1.80 (m, 6H), 1.79-1.50 (m, 3H), 1.2-1.1 (m, 3H). MS: (M^+H m/z = 392.5).

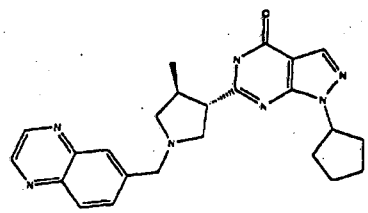
EXAMPLE 23

(a) 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



A solution of 6-[(3S,4S)1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (9.25g) in ethanol 100 mL was added to a Parr bottle. 2 mL of concentrated HCl followed by 3g of palladium hydroxide was added. The reaction mixture was placed on a hydrogenator under 45 psi of H_2 gas for 4h. The reaction mixture was filtered through Celite and concentrated to provide the title compound as an HCl salt. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 5.14-5.10 (m, 1H), 4.89-3.84 (m, 1H), 3.72-3.67 (m, 1H), 3.38-3.31 (m, 1H), 3.03-2.98 (m, 1H), 2.85-2.81 (m, 1H), 2.08-1.85 (m, 7H), 1.69-1.61 (m, 2H), 1.19-1.10 (m, 3H). MS: (M^+H m/z = 288.2).

(b) 1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



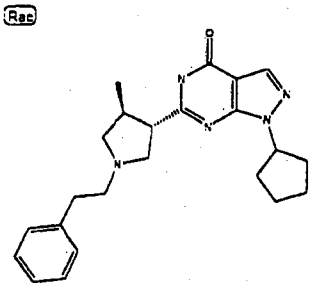
Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-

methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoxaline-6-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 8.07-7.93 (m, 3H), 5.15-5.08 (m, 1H), 4.00-3.87 (m, 2H), 3.37 (t, *J* = 8.7 Hz, 1H), 3.04 (d, *J* = 9.5 Hz, 1H), 2.85-2.84 (m, 1H), 2.66-2.62 (m, 1H), 2.46-2.42 (m, 1H), 2.11-1.92 (m, 7H), 1.71-1.63 (m, 2H), 1.20 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 430.1).

EXAMPLE 24

1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-phenylethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Rac

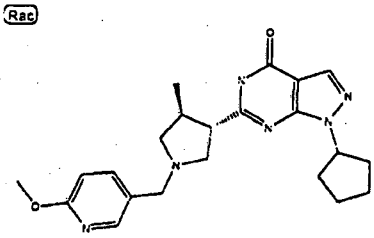


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-*trans*)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 2-phenylacetaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.32-7.19 (m, 5H), 5.18-5.11 (m, 1H), 3.44 (t, *J*= 8.7 Hz, 1H), 3.14 (d, *J* = 9.9 Hz, 1H), 2.90-2.78 (m, 5H), 2.56-2.52 (m, 1H), 2.40-2.39 (m, 1H), 2.14-1.89 (m, 7H), 1.73-1.67 (m, 2H), 1.19 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 392.1).

EXAMPLE 25

1-cyclopentyl-6-{(3,4-trans)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

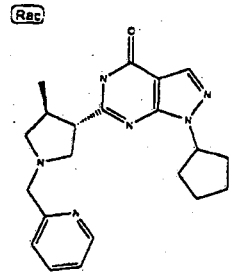
Rac



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (dd, *J* = 31.5, 2.5 Hz, 1H), 8.00 (s, 1H), 7.69 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 5.16-5.09 (m, 1H), 3.90 (s, 3H), 3.68 (d, *J* = 12.9 Hz, 1H), 3.55 (d, *J* = 12.9 Hz, 1H), 3.31 (t, *J*= 8.7 Hz, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.81-2.79 (m, 1H), 2.54-2.50 (m, 1H), 2.41-2.36 (m, 1H), 2.12-1.87 (m, 7H), 1.73-1.64 (m, 2H), 1.18 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 409.1).

EXAMPLE 26

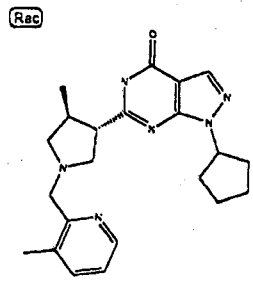
1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting picolinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.63-8.62 (m, 1H), 8.02 (s, 1H), 7.72-7.67 (m, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.20-7.17 (m, 1H), 5.18-5.10 (m, 1H), 4.03 (d, *J* =13.7 Hz, 1H), 3.75 (d, *J* =13.7 Hz, 1H), 3.41 (t, *J*= 8.3 Hz, 1H), 3.07 (d, *J* = 9.9 Hz, 1H), 2.83-2.82 (m, 1H), 2.58 (m, 1H), 2.46-2.40 (m, 1H), 2.13-1.89 (m, 7H), 1.74-1.64 (m, 2H), 1.21 (d, *J*= 7.1 Hz, 3H). MS: (M^+H m/z = 379.1).

EXAMPLE 27

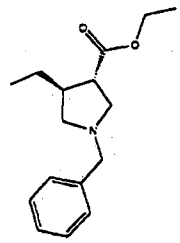
1-cyclopentyl-6-((3,4-trans)-4-methyl-1-[(3-methylpyridin-2-yl)methyl]pyrrolidin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 3-methylpicolinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.57 (t, *J* = 7.5, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 5.17-5.09 (m, 1H), 3.97 (d, *J* = 13.3 Hz, 1H), 3.68 (d, *J* = 13.3 Hz, 1H), 3.42 (t, *J*= 8.3 Hz, 1H), 3.05 (d, *J* = 9.9 Hz, 1H), 2.82-2.80 (m, 1H), 2.57-2.53 (m, 1H), 5.54 (s, 3H), 2.44-2.38 (m, 1H), 2.12-1.89 (m, 7H), 1.72-1.64 (m, 2H), 1.19 (d, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 393.1).

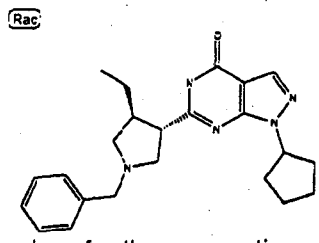
EXAMPLE 28

(a) (3,4-trans)-ethyl 1-benzyl-4-ethylpyrrolidine-3-carboxylate



Following the procedure for the preparation of (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate but substituting (E)-methyl pent-2-enoate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.19 (m, 5H), 4.15-4.08 (m, 2H), 3.65-3.52 (m, 2H), 2.82-2.71 (m, 3H), 2.60-2.55 (m, 1H), 2.38-2.24 (m, 2H), 1.59-1.50 (m, 1H), 1.47-1.38 (m, 1H), 1.23 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 262.2).

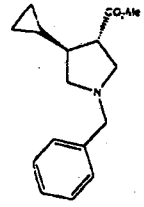
(b) 6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and (3,4-trans)-methyl 1-benzyl-4-ethylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.39-7.24 (m, 5H), 5.13-5.07 (m, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.58 (d, *J* = 12.9 Hz, 1H), 3.42 (t, *J*= 12.9 Hz, 1H), 3.33 (t, *J* = 8.7 Hz, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.86 (m, 1H), 2.46-2.42 (m, 1H), 2.19-1.44 (m,11H), 0.92 (t, *J*= 7.05 Hz, 3H). MS: (M^+H m/z = 392.1).

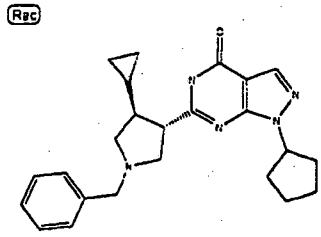
EXAMPLE 29

(a) (3,4-trans)-methyl-1-benzyl-4-cyclopropylpyrrolidine-3-carboxylate



Following the procedure for the preparation of (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate but substituting (E)-methyl 3-cyclopropylacrylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.20 (m, 5H), 3.66 (s, 3H), 3.64-3.54 (m, 2H), 2.87-2.81 (m, 2H), 2.77-2.70 (m, 2H), 2.47-2.43 (m, 1H), 1.84-1.78 (m, 1H), 0.87-0.79 (m, 1H), 0.45-0.36 (m, 2H), 0.20-0.06 (m, 2H). MS: (M^+H m/z = 260.2).

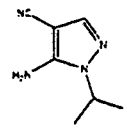
(b) 6-[(3,4-trans)-1-benzyl-4-cyclopropylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and (3,4-trans)-methyl-1-benzyl-4-cyclopropylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.38-7.31 (m, 4H), 7.27-7.23 (m, 1H), 5.14-5.10 (m, 1H), 3.78 (d, *J* = 12.4 Hz, 1H), 3.63 (d, *J* = 12.4 Hz, 1H), 3.32 (t, *J* = 8.7 Hz, 1H), 3.12-3.10 (m, 1H), 3.01 (d, *J* = 9.9 Hz, 1H), 2.59-2.57 (m, 1H), 2.20-1.87 (m, 8H), 1.71-1.65 (m, 2H), 0.86-0.84 (m, 1H), 0.52-0.48 (m, 2H), 0.19-0.09 (m, 2H). MS: (M^+H m/z = 393.1).

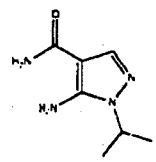
EXAMPLE 30

(a) 5-amino-1-isopropyl-1H-pyrazole-4-carbonitrile



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-isopropylhydrazine provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1H), 4.22-4.16 (m, 3H), 1.45 (d, *J* = 6.6 Hz, 6H). MS: (M^+H m/z = 151.1).

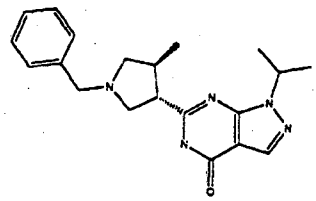
(b) 5-amino-1-isopropyl-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-

isopropyl-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.67 (s, 1H), 4.40-4.33 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 6H). MS: (M^+H m/z = 169.1).

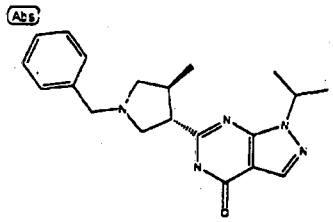
(c) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-isopropyl-1H-pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 7.38-7.22 (m, 5H), 5.07-5.04 (m, 1H), 3.77-3.64 (m, 2H), 3.12-3.08 (m, 1H), 2.99-2.91 (m, 3H), 2.67-2.63 (m, 1H), 2.27-2.25 (m, 1H), 1.48 (d, *J* = 7.1 Hz, 6H), 1.14 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 352.1).

EXAMPLE 31

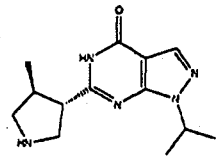
6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



The racemate was separated on Chiralcel OD chiral HPLC column, Mobile Phase 90/10 Heptane/EtOH, T_R = 8.917, to provide the enantiomer. 400 MHz ^{1}H NMR (CD_3OD) δ 7.98 (s, 1H), 7.38-7.33 (m, 2H), 7.33-7.29 (m, 2H), 7.26-7.22 (m, 1H), 5.07-5.02 (m, 1H), 3.77-3.64 (m, 2H), 3.12-3.07 (m, 1H), 2.99-2.91 (m, 3H), 2.67-2.63 (m, 1H), 2.29-2.25 (m, 1H), 1.48(d, *J* = 6.6 Hz, 6H), 1.14 (d, *J* = 6.6 Hz, 3H). MS: (M+H *m/z* 352.1).

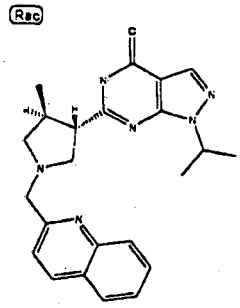
EXAMPLE 32

(a) 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting the 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 5.11-5.08 (m, 1H), 3.80-3.74 (m, 2H), 3.64-3.57 (m, 1H), 3.30-3.22 (m, 1H), 3.07-3.02 (m, 1H), 2.75-2.71 (m, 1H), 1.49 (dd, *J* = 6.6, 1.7 Hz, 6H), 1.15 (d, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 262.2).

(b) 1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinolin-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

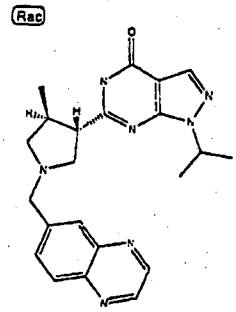


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoline-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.98 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.75-7.68 (m, 2H), 7.58-7.54 (m, 1H), 5.07-5.04 (m, 1H), 4.11-3.96 (m, 2H), 3.22-3.18 (m, 1H), 3.14-3.11 (m, 1H), 3.05-2.96 (m, 2H),

2.71-2.68 (m, 1H), 2.42-2.37 (m, 1H), 1.49 (q, J = 6.6 Hz, 6H), 1.17 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z 403.1).

EXAMPLE 33

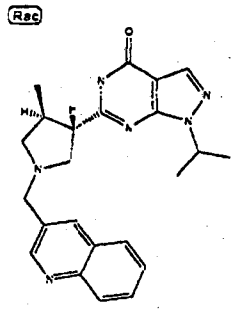
1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoxaline-6-carbaldehydeprovided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.84-8.81 (m, 2H), 8.04-8.00 (m, 2H), 7.96 (s, 1H), 7.91-7.88 (m, 1H), 5.09-5.02 (m, 1H), 4.01-3.87 (m, 2H), 3.14-3.93 (m, 4H), 2.72-2.66 (m, 1H), 2.39-2.34 (m, 1H), 1.47 (dd, J = 6.6, 1.2 Hz, 6H), 1.15 (d, J = 6.6 Hz, 3H). MS: (M+H m/z 404.1).

EXAMPLE 34

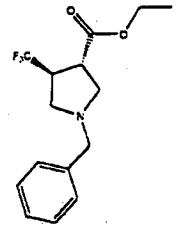
1-isopropyl-6-[(3,4-trans)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoline-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.87 (d, J = 2.1 Hz, 1H), 8.30 (d, J = 1.2 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.97 (s, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.74-7.69 (m, 1H), 7.60-7.56 (m, 1H), 5.06-4.99 (m, 1H), 3.97-3.87 (m, 2H), 3.13-3.09 (m, 1H), 3.05-3.02 (m, 2H), 2.97-2.93 (m, 1H), 2.73-2.66 (m, 1H), 2.39-2.35 (m, 1H), 1.46 (dd, J = 6.6, 2.3 Hz, 6H), 1.15 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 403.1).

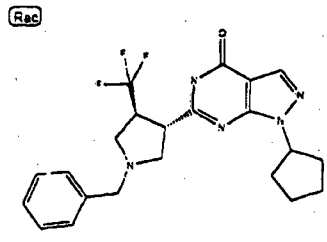
EXAMPLE 35

(a) (3,4-trans)-ethyl-1-benzyl-4-(trifluoromethyl)pyrrolidine-3-carboxylate



Following the procedure for the preparation of (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate but substituting (E)-methyl 4,4,4-trifluorobut-2-enoate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.22 (m, 5H), 4.16 (q, J = 7.1 Hz, 2H), 3.65-3.56 (m, 2H), 3.40-3.32 (m, 1H), 3.12-3.07 (m, 1H), 2.90-2.76 (m, 3H), 2.70-2.66 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H). MS: (M^+H m/z = 302.1).

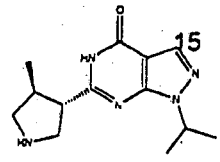
(b) 6-[(3,4-trans)-1-benzyl-4-(trifluoromethyl)pyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and (3,4-trans)-methyl 1-benzyl-4-(trifluoromethyl)pyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.38-7.26 (m, 5H), 5.15-5.11 (m, 1H), 3.83 (d, *J* = 12.5 Hz, 1H), 3.64 (d, *J* = 12.5 Hz, 1H), 3.44-3.41 (m, 1H), 3.34 (t, *J*= 9.1 Hz, 1H), 3.12-3.10 (m, 1H), 3.03 (d, *J* = 9.9 Hz, 1H), 2.70-2.65 (m, 1H), 2.55-5.50 (m, 1H), 2.11-1.93 (m, 4H), 1.72-1.66 (m, 2H), 0.86-0.83 (m, 2H). MS: (M^+H m/z = 432.0).

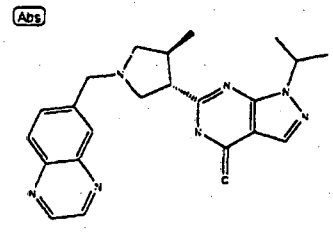
EXAMPLE 36

(a) 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H) one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting the 6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 5.11-5.08 (m, 1H), 3.80-3.74 (m, 2H), 3.64-3.57 (m, 1H), 3.30-3.22 (m, 1H), 3.07-3.02 (m, 1H), 2.75-2.71 (m, 1H), 1.49 (dd, *J* = 6.6, 1.7 Hz, 6H), 1.15 (d, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 262.2).

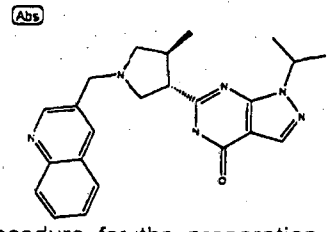
(b) 1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoxaline-6-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 11.0 (brs, 1H), 8.81 (s, 2H), 8.13 (d, J = 8.7, 1H), 8.01-7.92 (m, 3H), 5.01-4.94 (m, 1H), 4.01-3.88 (m, 2H), 3.37 (t, J = 8.3, 1H), 3.05 (d , J = 9.9, 1H), 2.86-2.85 (m, 1H), 2.70-2.68 (m, 1H), 2.49-2.44 (m, 1H), 2.07-2.01 (m, 1H), 1.48 (dd, J = 15.3, 6.6 Hz, 6H), 1.20 (d, J = 7.05 Hz, 3H). MS: (M+H m/z 404.1).

EXAMPLE 37

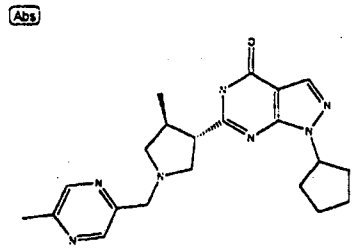
1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoline-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 11.0 (brs, 1H), 8.87 (d, J = 2.1 Hz, 1H), 8.29 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 7.90-7.88 (m, 1H), 7.70-7.66 (m, 1H), 7.56-7.51 (m, 1H), 5.01-4.92 (m, 1H), 4.03-3.83 (m, 2H), 3.40 (t, J = 8.7 Hz, 1H), 3.07 (d, J = 9.5 Hz, 1H), 2.89-2.86 (m, 1H), 2.68-2.67 (m, 1H), 2.48-2.47 (m, 1H), 2.08-2.02 (m, 1H), 1.48 (dd, J = 6.6, 16.59 Hz, 6H), 1.20 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 403.1).

EXAMPLE 38

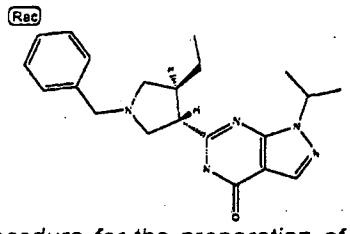
1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 5-methylpyrazine-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.53 (s, 1H), 8.01 (s, 1H), 5.16-5.05 (m, 1H), 4.02 (d, *J* = 14.1 Hz, 1H), 3.74 (d, *J* = 14.1 Hz, 1H), 3.45-3.41 (m, 1H), 3.38 (t, *J* = 8.3 Hz, 1H), 3.08 (d, *J* = 9.9 Hz, 1H), 2.84-2.83 (m, 1H), 2.62-2.54 (m, 1H), 2.52 (s, 3H), 2.47-2.40 (m, 1H), 2.14-1.89 (m, 6H), 1.71-1.64 (m, 2H), 1.24-1.16 (m, 3H). MS: (M^+H m/z = 394.1).

EXAMPLE 39

6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

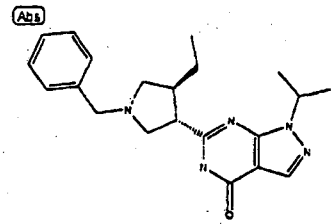


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-isopropyl-1H-pyrazole-4-carboxamideand (3,4-trans)-methyl 1-benzyl-4-ethylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.01 (s, 1H), 7.38-7.22 (m, 5H), 5.06-5.01 (m, 1H), 3.76-3.64 (m, 2H), 3.12 (t, *J* = 8.71 Hz, 1H), 3.00-2.91 (m, 2H), 2.87-2.82 (m, 1H), 2.51-2.47 (m, 1H), 2.30-2.26 (m,

1H), 1.60-1.50 (m, 2H), 1.49 (d, J = 7.05 Hz, 6H), 3.08 (d, J = 7.5 Hz, 3H). MS: (M^+H m/z = 366.1).

EXAMPLE 40

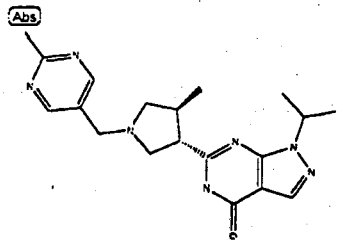
6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



The racemate was separated on Chiralcel OJ chiral HPLC column, Mobile Phase 80/20 Heptane/EtOH, T_R = 9.177, to provide the enantiomer. 400 MHz ^{1}H NMR (CD_3OD) δ 8.01 (s, 1H), 7.38-7.22 (m, 5H), 5.06-5.01 (m, 1H), 3.76-3.64 (m, 2H), 3.12 (t, J = 8.71 Hz, 1H), 3.00-2.91 (m, 2H), 2.87-2.82 (m, 1H), 2.51-2.47 (m, 1H), 2.30-2.26 (m, 1H), 1.60-1.50 (m, 2H), 1.49 (d, J = 7.05 Hz, 6H), 3.08 (d, J = 7.5 Hz, 3H). MS: (M^+H m/z = 366.2).

EXAMPLE 41

1-isopropyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

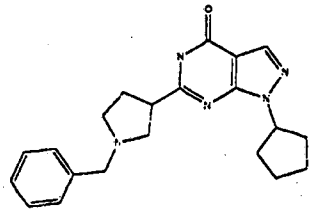


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 2-methylpyrimidine-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.68 (s, 2H), 7.97 (s, 1H), 5.08-5.01 (m, 1H), 3.78-3.68 (m,

2H), 3.08-2.92 (m, 4H), 2.74-2.67 (m, 1H), 2.65 (s, 3H), 2.36-2.32 (m, 1H), 1.48 (d, J = 6.6 Hz, 6H), 1.15 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 368.1).

EXAMPLE 42

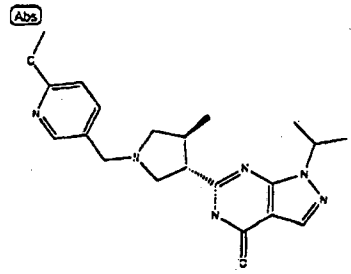
6-(1-benzylpyrrolidin-3-yl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and methyl 1-benzylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^1H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.39-7.32 (m, 4H), 7.27-7.23 (m, 1H), 5.12-5.09 (m, 1H), 3.84 (d, J =12.4 Hz, 1H), 3.61 (d, J =12.4 Hz, 1H), 3.30-3.26 (m, 1H), 3.18-3.14 (m, 1H), 3.01 (d, J = 9.9 Hz, 1H), 2.45-2.32 (m, 3H), 2.11-1.90 (m, 7H), 1.71-1.65 (m, 2H). MS: (M^+H m/z = 364.1).

EXAMPLE 43

1-isopropyl-6-((3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

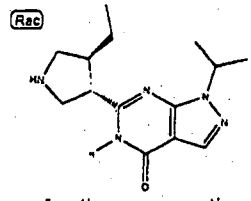


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 6-

methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 2H), 7.72 (m, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 3.73-3.53 (m, 2H), 3.39-3.33 (m, 1H), 3.30 (m, 1H), 2.8 (m, 1H), 2.55-2.40 (m, 1H), 1.9 (m, 1H), 1.57-1.53 (m, 2H), 1.52-1.47 (m, 6H), 1.19 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 383.2).

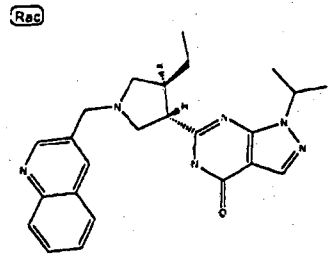
EXAMPLE 44

(a) 6-((3,4-trans)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting the 6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 5.10 (m, 1H), 3.78-3.60 (m, 3H), 3.32-3.28 (m, 1H), 3.10 (m, 1H), 2.62 (m, 1H), 1.65 (m, 1H), 1.58 (m, 1H), 1.49 (dd, *J* = 6.6, 1.7 Hz, 6H), 0.97 (t, *J* = 7.5 Hz, 3H). MS: (M^+H m/z = 276.1).

(b) 6-[(3,4-trans)-4-ethyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

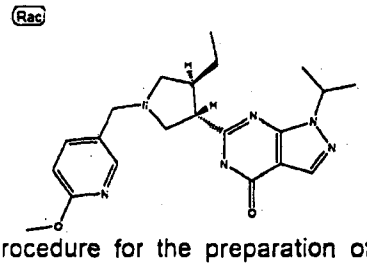


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-((3,4-trans)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoline-3-

carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.86 (d, J = 2.1 Hz, 1H), 8.29 (d, J = 1.7 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.97 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.73-7.68 (m, 1H), 7.59-7.55 (m, 1H), 5.05-4.98 (m, 1H), 3.94-3.85 (m, 2H), 3.13-3.09 (m, 1H), 3.02-2.94 (m, 3H), 2.57-2.52 (m, 1H), 2.39-2.34 (m, 1H), 1.58-1.48 (m, 2H), 1.48 (d, J = 6.6 Hz, 6H) 10.87 (t, J = 7.05 Hz, 3H). MS: (M^+H m/z = 417.0).

EXAMPLE 45

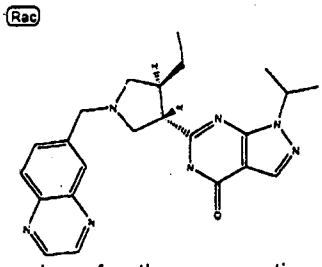
6-{(3,4-trans)-4-ethyl-1-[(6-methoxypyridin-3-yl)methyl]pyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-((3,4-trans)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 6-methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.83 (brs, 1H), 8.02 (d, J = 2.1 Hz, 1H), 8.00 (s, 1H), 7.69 (dd, J = 8.7, 2.1 Hz, 1H), 6.77 (d, J = 8.3 Hz, 1H), 4.98-4.94 (m, 1H), 3.89 (s, 3H), 3.69-3.54 (m, 2H), 3.29 (t, J = 8.5 Hz, 1H), 2.98 (d, J = 9.9 Hz, 1H), 2.88-2.87 (m, 1H), 2.55 (m, 1H), 2.18 (m, 1H), 1.91 (m, 1H), 1.60-1.55 (m, 1H), 1.51-1.47 (m, 7H), 0.91 (t, J = 7.5 Hz, 3H). MS: (M^+H m/z = 397.0).

EXAMPLE 46

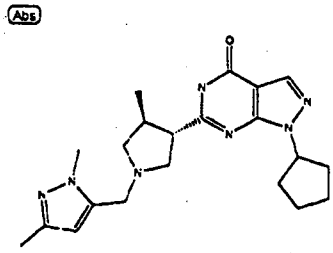
6-[(3,4-trans)-4-ethyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-((3,4-trans)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoxaline-6-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.83 (brs, 1H), 8.81 (s, 2H), 7.79 (d, J = 2.5 Hz, 1H), 8.15-7.92 (m, 3H), 4.99-4.92 (m, 1H), 3.98-3.86 (m, 2H), 3.35 (t, J = 8.7 Hz, 1H), 3.04 (d, J = 9.9 Hz, 1H), 2.92-2.91 (m, 1H), 2.61-2.57 (m, 1H), 2.25-2.2 (m, 1H), 2.02 (t, J = 8.7 Hz, 1H), 1.64-1.52 (m, 1H), 1.50-1.45 (m, 7H), 0.91 (t, J = 7.5 Hz, 3H). MS: (M^+H m/z = 418.1).

EXAMPLE 47

1-cyclopentyl-6-[(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

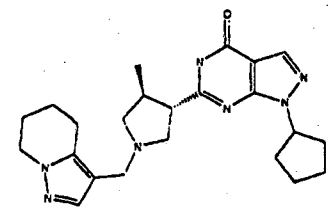


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 1,3-dimethyl-1H-pyrazole-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 5.95-5.94 (m, 1H), 5.14-5.09 (m, 1H), 3.87 (s, 3H), 3.81 (s, 1H), 3.66 (q, J = 14.5 Hz, 2H), 3.33 (t, J = 8.3 Hz, 1H), 3.03

(d, J = 9.9 Hz, 1H), 2.84-2.82 (m, 1H), 2.59-2.55 (m, 1H), 2.44-2.41 (m, 1H), 2.20-2.19 (m, 3H), 2.12-1.90 (m, 5H), 1.70-1.65 (m, 2H), 1.25-1.18 (m, 3H). MS: (M^+H m/z = 396.1).

EXAMPLE 48

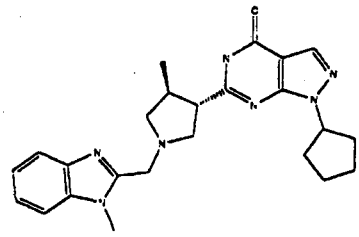
1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl) pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.35 (s, 1H), 5.16-5.09 (m, 1H), 4.11-4.06 (m, 2H), 3.68 (d, J = 13.3 Hz, 1H), 3.57 (d, J = 13.3 Hz, 1H), 3.32 (t, J = 8.7 Hz, 1H), 3.00 (d, J = 9.9 Hz, 1H), 2.94-2.80 (m, 2H), 2.78-2.77 (m, 1H), 2.49-2.45 (m, 1H), 2.38-2.33 (m, 1H), 2.11-1.83 (m, 11H), 1.73-1.61 (m, 2H), 1.17 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 422.1).

EXAMPLE 49

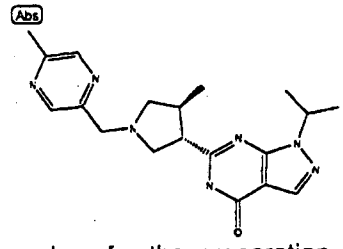
1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 1-methyl-1H-benzo[d]imidazole-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 7.73 (m, 1H), 7.35 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.29-7.21 (m, 2H), 5.13-5.09 (m, 1H), 4.11-4.06 (m, 2H), 3.97 (s, 3H), 3.37 (t, *J* = 8.3 Hz, 1H), 3.06 (d, *J* = 10.4 Hz, 1H), 2.88-2.85 (m, 1H), 2.77-2.73 (m, 1H), 2.16-1.92 (m, 8H), 1.70-1.66 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 432.1).

EXAMPLE 50

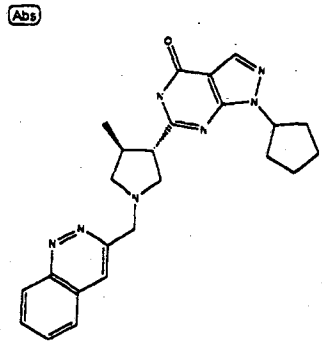
1-isopropyl-6-[(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 5-methylpyrazine-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 11.4 (brs, 1H), 8.49 (s, 1H), 8.44 (s, 1H), 7.99 (s, 1H), 5.00-4.93 (m, 1H), 4.00-3.97 (m, 1H), 3.78-3.67 (m, 1H), 3.33 (t, *J* = 8.3 Hz, 1H), 3.04 (d, *J* = 9.9 Hz, 1H), 2.85-2.82 (m, 1H), 2.65-2.61 (m, 1H), 2.49 (s, 3H), 2.48-2.41 (m, 1H), 2.13 (t, *J* = 8.5 Hz, 1H), 1.46 (dd, *J* = 11.6,6.6 Hz, 6H), 1.17 (d, *J* = 7.05 Hz, 3H). MS: (M^+H m/z = 368.1).

EXAMPLE 51

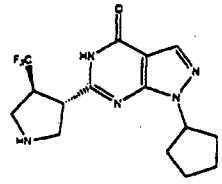
6-[(3S,4S)-1-(cinnolin-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and cinnoline-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.49 (d, *J* = 8.7 Hz, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.83-7.81 (*m*, 1H), 7.79-7.71 (m, 1H), 5.16-5.09 (m, 1H), 4.47-4.44 (m, 1H), 4.35-4.32 (m, 1H), 3.49-3.45 (m, 2H), 3.10-3.07 (m, 1H), 2.87-2.71 (m, 2H), 2.49-2.48 (m, 1H), 2.23 (m, 1H), 2.11-1.87 (m, 5H), 1.73-1.63 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 3H). MS: (M^+H m/z = 430.1).

EXAMPLE 52

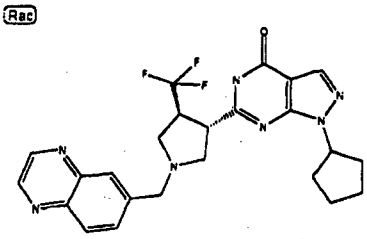
(a) 1-cyclopentyl-6-[(3,4-trans)-4-(trifluoromethyl)pyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting the 6-[(3,4-trans)-1-benzyl-4-(trifluoromethyl)pyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 7.98 (s, 1H), 5.23 (m, 1H), 3.73 (m, 1H), 3.42 (m, 2H), 3.10 (m, 2H), 2.19-1.92 (m, 7H), 1.75 (m, 2H), 1.23-1.19 (m, 3H).

(b) 1-cyclopentyl-6-[(3,4-trans)-1-(quinoxalin-6-ylmethyl)-4-(trifluoromethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

(Rac)

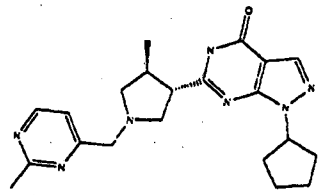


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3,4-trans)-4-(trifluoromethyl)pyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and *quinoxaline-6-carbaldehyde provided the title compound.* 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.99 (m, 1H), 7.86-7.83 (m, 1H), 5.13-5.10 (m, 1H), 4.88 (s, 1H), 3.96-3.88 (m, 2H), 3.50-3.35 (m, 2H), 3.17 (t, J = 9.9 Hz, 1H), 3.03-2.99 (m, 1H), 2.92-2.88 (m, 1H), 2.79-2.75 (m, 1H), 2.11-1.90 (m, 6H), 1.71-1.65 (m, 1H).

EXAMPLE 53

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

(Abs)

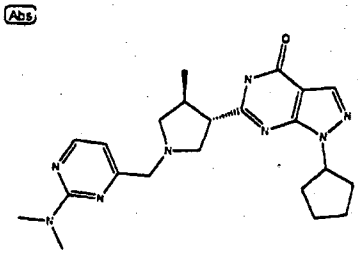


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 2-methylpyrimidine-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.60 (d, J = 5.4 Hz, 1H), 8.03 (s, 1H), 7.24 (s, 1H), 5.18-5.10 (m, 1H), 3.97-3.94 (m, 1H), 3.72-3.68 (m, 1H), 3.40 (t, J = 8.3 Hz, 1H), 3.15

(d, J = 9.5 Hz, 1H), 2.89 (m, 1H), 2.73 (s, 3H), 2.68-2.63 (m, 1H), 2.53-2.47 (m, 1H), 2.15-1.89 (m, 7H), 1.74-1.65 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 394.1).

EXAMPLE 54

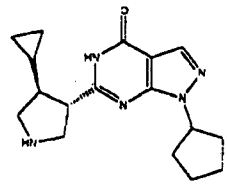
1-cyclopentyl-6-[(3S,4S)-1-{[2-(dimethylamino)pyrimidin-4-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 2-(dimethylamino)pyrimidine-4-carbaldehydeprovided the title compound. 400 MHz ^1H NMR ($CDCl_3$) δ 8.24-8.21 (m, 1H), 8.00-7.99 (m, 1H), 6.52-6.50 (m, 1H), 5.13-5.10 (m, 1H), 3.72-3.68 (m, 1H), 3.56-3.52 (m, 1H), 3.46-3.40 (m, 3H), 3.17-3.11 (m, 7H), 2.84-2.82 (m, 1H), 2.64-2.60 (m, 1H), 2.44-2.38 (m, 1H), 2.06-1.92 (m, 5H), 1.66-1.65 (m, 2H), 1.20-1.16 (m, 3H). MS: (M^+H m/z = 423.1).

EXAMPLE 55

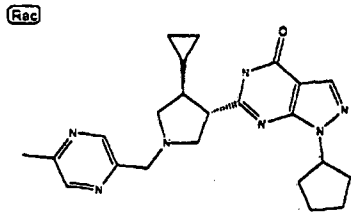
(a) 1-cyclopentyl-6-[(3,4-trans)-4-cyclopropylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-[(3,4-trans)-1-benzyl-4-cyclopropylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-

4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.08-7.94 (m, 1H), 5.17-5.10 (m, 1H), 3.39-3.34 (m, 1H), 3.29-3.28 (m, 2H), 3.17-3.14 (m, 1H), 2.13-1.91 (m, 7H), 1.78-1.67 (m, 3H), 0.82 (m, 1H), 0.47-0.44 (m, 2H), 0.13-0.08 (m, 2H). MS: (M^+H m/z = 314.2).

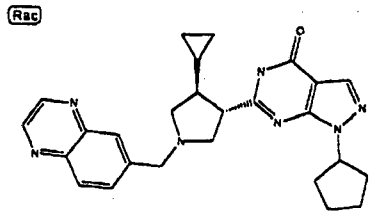
(b) 1-cyclopentyl-6-{(3,4-trans)-4-cyclopropyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 1-cyclopentyl-6-[(3,4-trans)-4-cyclopropylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 5-methylpyrazine-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 0.8 Hz, 1H), 8.46 (s, 1H), 8.00 (s, 1H), 5.14-5.10 (m, 1H), 4.04-4.01 (m, 1H), 3.78-3.75 (m, 1H), 3.35 (t, J = 8.7 Hz, 1H), 3.15-3.09 (m, 2H), 2.66-2.64 (m, 1H), 2.52 (s, 3H), 2.38 (t, J = 8.7 Hz, 1H), 2.11-2.01 (m, 3H), 1.96-1.91 (m, 2H), 1.73-1.65 (m, 2H), 1.24-1.20 (m, 1H), 0.59-0.83 (m, 2H), 0.53-0.49 (m, 2H), 0.23-0.11 (m, 2H). MS: (M^+H m/z = 420.1).

EXAMPLE 56

1-cyclopentyl-6-[(3,4-trans)-4-cyclopropyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

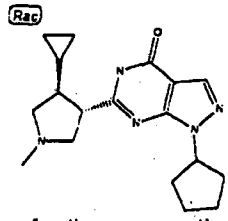


Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 1-cyclopentyl-6-[(3,4-trans)-4-cyclopropylpyrrolidin-3-yl]-1H-pyrazolo[3,4-

d]pyrimidin-4(5H)-one and quinoxaline-6-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 2H), 8.14 (d, *J* = 8.7 Hz, 1H), 8.00 (s, 2H), 7.96-7.94 (m, 1H), 5.16-5.09 (m, 1H), 3.98-3.95 (m, 2H), 3.35 (t, *J* = 8.3 Hz, 1H), 3.15-3.08 (m, 2H), 2.70 (m, 1H), 2.27 (m, 1H), 2.15-1.88 (m, 6H), 1.74-1.62 (m, 3H), 0.91-0.87 (m, 1H), 0.55-0.47 (m, 2H), 0.21-0.09 (m, 2H). MS: (M^+H m/z = 456.1).

EXAMPLE 57

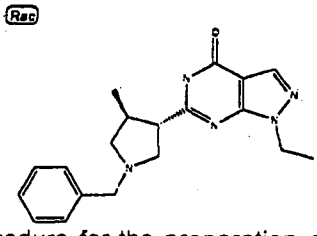
1-cyclopentyl-6-[(3,4-trans)-4-cyclopropyl-1-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 1-cyclopentyl-6-[(3,4-trans)-4-cyclopropylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and formaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 5.19-5.11 (m, 1H), 3.31 (d, *J* = 8.7 Hz, 1H), 3.14-3.13 (m, 1H), 3.06 (d, *J* = 9.9 Hz, 1H), 2.57 (m, 1H), 2.43 (s, 3H), 2.14-1.91 (m, 7H), 1.75-1.64 (m, 3H), 0.91-0.82 (m, 1H), 0.53-0.50 (m, 2H), 0.20-0.14 (m, 2H). MS: (M^+H m/z = 328.2).

EXAMPLE 58

6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-ethyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

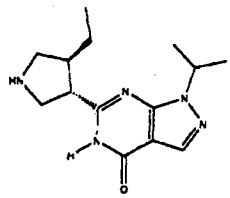


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-

d]pyrimidin-4-one but substituting 5-amino-1-ethyl-1H-pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.42-7.27 (m, 5H), 4.38-4.30 (m, 2H), 3.83-3.80 (m, 1H), 3.63-3.59 (m, 1H), 3.49-3.35 (m, 1H), 2.99 (d, *J* = 10.3 Hz, 1H), 2.83-2.80 (m, 1H), 2.55-2.50 (m, 1H), 2.44-2.378 (m, 1H), 1.95-1.90 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 10.3 Hz, 3H). MS: (M^+H m/z = 338.1).

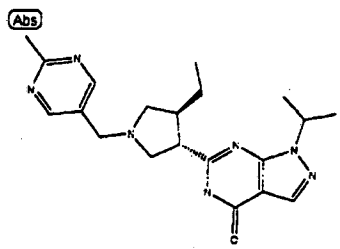
EXAMPLE 59

(a) 6-((3S,4S)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 5.10 (m, 1H), 3.78-3.60 (m, 3H), 3.32-3.28 (m, 1H), 3.10 (m, 1H), 2.62 (m, 1H), 1.65 (m, 1H), 1.58 (m, 1H), 1.49 (dd, *J* = 6.6, 1.7 Hz, 6H), 0.97 (t, *J* = 7.5 Hz, 3H). MS: (M^+H m/z = 276.1).

(b) 6-{(3,4-trans)-4-ethyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

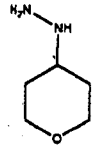


Following the procedure for the preparation of 1-cyclopentyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-((3S,4S)-4-ethylpyrrolidin-3-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-

4(5H)-one and 2-methylpyrimidine-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.8 (brs, 1H), 8.62 (s, 2H), 8.01 (s, 1H), 5.00-4.93 (m, 1H), 3.66 (s, 2H), 3.25-3.20 (m, 1H), 3.02 (d, *J* = 9.9 Hz, 1H), 2.95-2.92 (m, 1H), 2.70 (s, 3H), 2.62-2.58 (m, 1H), 2.28-2.23 (m, 1H), 1.98 (t, *J* = 8.7 Hz, 1H), 1.62-1.52 (m, 1H), 1.48 (t, *J* = 6.6 Hz, 6H), 1.46-1.42 (m, 1H), 3.08 (t, *J* = 7.5 Hz, 3H). MS: (M^+H m/z = 382.2).

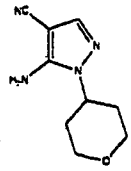
EXAMPLE 60

(a) 1-(tetrahydro-2H-pyran-4-yl)hydrazine



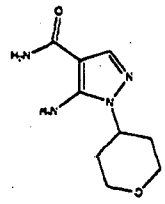
To a solution of tetrahydropyran-4-one (71.6 g, 715 mmol) in methanol (2 L) was added tert-butylcarbazate (100 g, 758 mmol) at ambient temp. The mixture was stirred at ambient temp for 20 h. The reaction mixture was concentrated under reduced pressure to dryness to afford a white solid (154 g). To a suspension of the white solid (154 g, 715 mmol) in water (1 L) was added acetic acid (500 mL, 8.73 mol) and the mixture was stirred for 30 min to get a clear solution. To this solution, solid $NaCNBH_3$ (44.5 g, 708 mmol) was added portion-wise. The mixture was stirred at ambient temp for 2 h. The mixture was then transferred to a 12 L flask, cooled to 0 °C, and quenched with 1N NaOH (8.73 L, 8.73 mol). The mixture was extracted with CH_2Cl_2 (3 x 3 L) and dried over Na_2SO_4. The organic layer was filtered and concentrated to afford a white solid (164 g, contains ~15% of N-acetyl-N'-Boc-hydrazine derivative). Chromatography [silica, ethyl acetate/MeOH (95:5] gave 94 g of 90% pure boc-hydrazine. A solution of boc-hydrazine (50 g, 231 mmol) in methanol (500 mL) was added a solution of HCl in dioxane (462 mL, 1.85 mol, 4.0 M). The mixture was stirred at ambient temp overnight. Concentration of the reaction mixture under reduced pressure afforded the title compound as a white solid (43 g, 98%). 400 MHz ^{1}H NMR (DMSO) δ 3.85-3.82 (m, 2H), 3.27-3.21 (m, 2H), 3.13-3.05 (m, 1H), 1.88-1.84 (m, 2H), 1.48-1.38 (m, 2H). MS: (M+H m/z = 117.2).

(b) 5-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile



To a mixture of 1-(tetrahydro-2H-pyran-4-yl)hydrazine di-hydrogen chloride (18g, 96 mmol) in 200 mL of EtOH was added Et_3N (30g, 40 mL, 288 mmol) at 0°C (ice bath). The resulting mixture was stirred for 1 h, then a solution of 2-(ethoxymethylene)malononitrile (12 g, 96 mmol) in 100 mL of EtOH was added slowly to keep the reaction temp below 5 °C. This mixture was stirred at ambient temp overnight and then heated to reflux for 2 hr. After removal of the solvent under vacuum, the residue was washed with 300 mL of water. The solid was collected, washed with additional 200 mL of water, 200 mL of 1:1 of hexane and ether, dried to give 17 g of yellow solid. 400 MHz ^{1}H NMR (CD_3OD) δ 7.71 (s, 1H), 4.29-4.21 (m, 1H), 4.02 (dd, J = 11.6, 4.6 Hz, 2H), 3.28 (t, J = 1.7 Hz, 2H), 2.12-2.02 (m, 2H), 1.80-1.76 (m, 2H). MS: (M^+H m/z = 193.1).

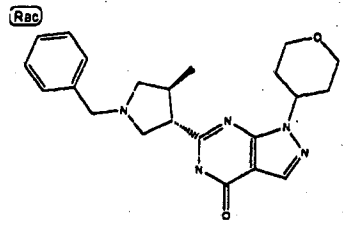
(c) 5-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide



A stirred solution of 5-amino-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile (~228 mmol) in ethanol (300 mL) was treated with 35% aqueous H_2O_2 (100 mL) followed by aqueous ammonia (300 mL). The reaction mixture was stirred for 48 h at ambient temp and then quenched with aq saturated sodium thiosulfate (800 mL) and concentrated under reduced pressure to remove most of the ethanol. The resulting solid was removed by filtration and washed with water (2 x 200 mL) and ether (2 x 150 mL). The solid was dried in vacuo to constant weight (31 g, 65% yield for 2 steps). 400 MHz ^{1}H NMR

(CD_3OD) δ 7.67 (s, 1H), 4.27-4.21 (m, 1H), 4.03 (dd, *J* = 11.6, 4.6 Hz, 2H), 3.28 (t, *J* = 1.7 Hz, 2H), 2.14-2.04 (m, 2H), 1.81-1.78 (m, 2H). MS: (M^+H m/z = 382.2).

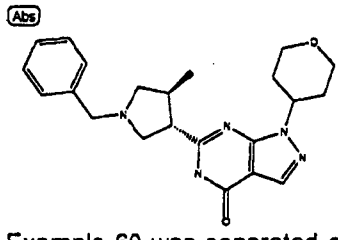
(d) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a mixture of 5-amino-1-(tetrahydro-2H-pyran-4-yl-1H-pyrazole-4-carboxamide (6.0 g, 28.54 mmol) and (3,4-trans)-methyl 1-benzyl-4-methylpyrrolidine-3-carboxylate (13.3 g, 57.08 mmol) was added molecular sieves (pellets). To the stirred mixture was added a 1.0 M solution of *t*-BuOK in THF (57.1 ml, 57.08 mmol) and the resulting mixture was heated at reflux under an atmosphere of nitrogen with vigorous stirring overnight. Analysis of the reaction mixture by LC/MS indicated consumption of the starting material. The reaction mixture was cooled to ambient temp and solids were removed by filtration. The solids were washed with EtOAc (2 x) and the combined filtrates were concentrated under reduced pressure. The remainder was partitioned between CH_2Cl_2 and H_2O and the aqueous and organic layers were separated. The aqueous phase was extracted with CH_2Cl_2 (1 x) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The remaining residue was purified by chromatography (silica gel, 1 % Et_3N in EtOAc) to afford the title compound (7.8 g, 70% yield) as an off-white solid. 400 MHz ^1H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.39-7.25 (m, 6H), 4.83-4.75 (m, 1H), 4.14-4.09 (m, 2H), 3.82 (m, 1H), 3.62-3.54 (m, 3H), 3.39-3.37 (m, 1H), 3.00 (m, 1H), 2.83 (m, 1H), 2.66-2.27 (m, 4H), 2.10-1.83 (m, 3H), 1.20 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 394.2).

EXAMPLE 61

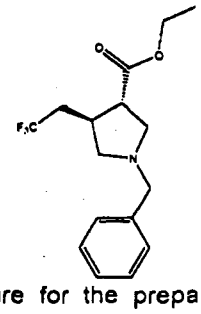
6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



The racemate of Example 60 was separated on Chiralcel OD-H chiral HPLC column, Mobile Phase 70/30 Heptane/EtOH, T_R = 11.465, to provide the enantiomer. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.39-7.25 (m, 6H), 4.82-4.76 (m, 1H), 4.14-4.09 (m, 2H), 3.82-3.79 (m, 1H), 3.62-3.54 (m, 3H), 3.37 (d, *J* = 8.7 Hz, 1H), 3.00 (d, *J* = 9.9 Hz , 1H), 2.79 (dd, *J* = 6.3, 2.5 Hz , 1H), 2.52-2.48 (m, 1H), 2.42-2.30 (m, 3H), 1.94-1.82 (m, 3H), 1.20 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 394.2).

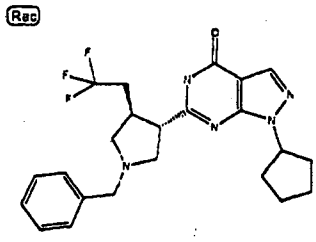
EXAMPLE 62

(a) (3,4-trans)-ethyl-1-benzyl-4-(2,2,2-trifluoroethyl)pyrrolidine-3-carboxylate



Following the procedure for the preparation of (3,4-trans)-methyl-1-benzyl-4-methylpyrrolidine-3-carboxylate but substituting (E)-methyl-5,5,5-trifluoropent-2-enoate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.21 (m, 5H), 4.18-4.10 (m, 2H), 3.67-3.55 (m, 2H), 2.90-2.63 (m, 4H), 2.43-2.34 (m, 2H), 2.24-2.15 (m, 1H), 1.27-1.22 (m, 3H), 0.88-0.85 (m, 1H).

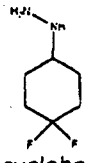
(b) 6-[(3,4-trans)-1-benzyl-4-(2,2,2-trifluoroethyl)pyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and (3,4-trans)-ethyl-1-benzyl-4-(2,2,2-trifluoroethyl) pyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.36-7.26 (m, 5H), 5.12-5.08 (m, 1H), 3.85-3.81 (m, 1H), 3.60-3.57 (m, 1H), 3.42 (t, J = 8.3 Hz, 1H), 3.02-2.96 (m, 2H), 2.64 (m, 1H), 2.53-2.44 (m, 2H), 2.34-1.89 (m, 6H), 1.81-1.62 (m, 4H).

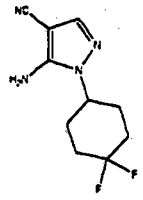
EXAMPLE 63

(a) 1-(4,4-difluorocyclohexyl)hydrazine



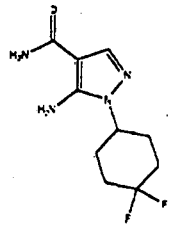
To a solution of 4,4-difluorocyclohexanol (0.9g) in toluene was added triphenyl phosphine (2.6g) and di-*t*-butyldiazacarboxalate (1.82g) and the reaction mixture stirred for 18 h. The reaction mixture was concentrated and methanol was added (13mL). To the methanol solution HCl in dioxane (4M, 13 mL) was added. The reaction mixture was stirred for 3 h and concentrated. The reaction mixture was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted 3x with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated. The title compound was used without purification in the preparation of 5-amino-1-(4,4-difluorocyclohexyl)-1H-pyrazole-4-carbonitrile. 400 MHz ^{1}H NMR (CD_3OD) δ 2.15-2.07 (m, 4H), 2.00-1.81 (m, 2H), 1.68-1.58 (m,2H). (M^+H m/z = 279.0).

(b) 5-amino-1-(4,4-difluorocyclohexyl)-1H-pyrazole-4-carbonitrile



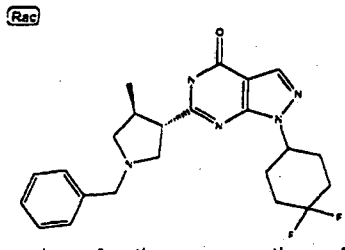
Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-(4,4-difluorocyclohexyl)hydrazine provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 1H), 3.90 (m, 1H), 2.40-1.00 (m, 8H).

(c) 5-amino-1-(4,4-difluorocyclohexyl)-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-(4,4-difluorocyclohexyl)-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.01 (s, 1H), 4.19 (m, 1H), 2.22-1.90 (m, 8H).

(d) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(4,4-difluorocyclohexyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

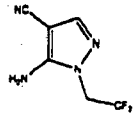


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-(4,4-difluorocyclohexyl)-1H-pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR

($CDCl_3$) δ 8.00 (s, 1H), 7.40-7.25 (m, 5H), 4.73-4.67 (m, 1H), 3.85-3.82 (m, 1H), 3.64-3.61 (m, 1H), 3.38 (t, J = 8.7 Hz, 1H), 3.00 (m, 1H), 2.83 (m, 1H), 2.56-2.52 (m, 1H), 2.43-2.25 (m, 5H), 2.04-1.90 (m, 5H), 1.20 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 428.1).

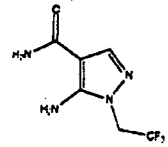
EXAMPLE 64

(a) 5-amino-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carbonitrile



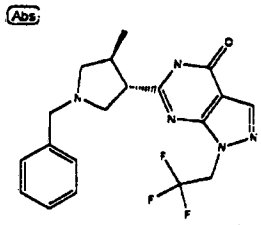
Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-(2,2,2-trifluoroethyl)hydrazine provided the title compound. 400 MHz ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H), 4.59 (m, 2H), 4.40 (brs, 2H).

(b) 5-amino-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^1H NMR (DMSO) δ 7.75 (s, 1H), 7.30 (brs, 1H), 6.78 (brs, 1H) 6.58 (m, 2H), 4.88 (m, 2H).

(c) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2,2,2-trifluoroethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one]

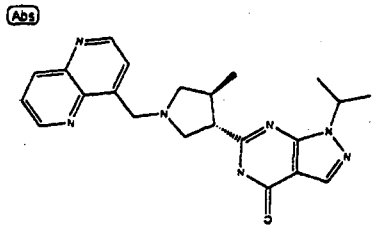


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-

d]pyrimidin-4-one but substituting 5-amino-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.59-7.57 (m, 2H), 7.44-7.41 (m, 3H), 4.96-4.88 (m, 2H), 4.22-4.11 (m, 2H), 3.57-3.37 (m, 4H), 2.85 (m, 2H), 1.26-1.23 (m, 3H). MS: (M^+H m/z = 392.1).

EXAMPLE 65

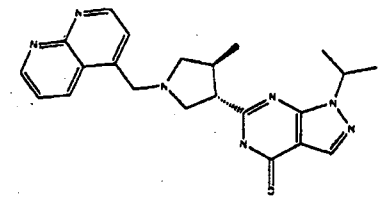
1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,5-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 1,5-naphthyridine-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 9.09-9.08 (m, 1H), 8.95-8.87 (m, 1H), 8.44-8.39 (m, 1H), 8.00 (s, 1H), 7.73-7.70 (m, 1H), 7.67-7.64 (m, 1H), 5.00-4.96 (m, 1H), 4.56-4.53 (m, 1H), 4.33-4.29 (m, 1H), 3.34 (t, J = 8.3 Hz , 1H), 3.19 (d, J = 9.5 Hz , 1H), 2.91-2.82 (m, 2H), 2.47-2.43 (m, 1H), 2.12 (t, J = 8.3 Hz, 1H), 1.48 (dd, J = 9.9, 6.6 Hz, 6H), 1.18 (d, J = 7.1 Hz, 3H). MS: (M^+H m/z = 404.2).

EXAMPLE 66

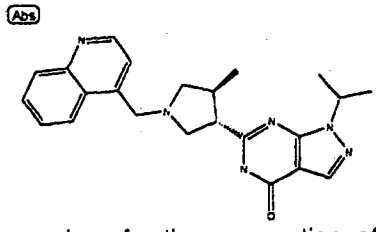
1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,8-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one]



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 1,8-naphthyridine-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, *J* = 4.1, 1.7 Hz, 1H), 9.07 (d, *J* = 4.6 Hz, 1H), 8.69 (dd, *J* = 8.3, 1.66 Hz, 1H), 7.99 (s, 1H), 7.69-7.65 (m, 1H), 7.46 (d, *J* = 4.6 Hz, 1H), 5.00-4.93 (m, 1H), 4.14 (s, 3H), 3.26 (t, *J* = 8.3 Hz , 1H), 3.03 (d, *J* = 9.5 Hz , 1H), 2.92-2.90 (m, 1H), 2.80-2.76 (m, 1H), 2.52-2.43 (m, 1H), 1.50-1.46 (m, 6H), 1.20 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 404.1).

EXAMPLE 67

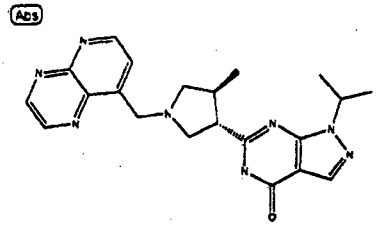
1-isopropyl-6-[3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and quinoline-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.63 (brs, 1H), 8.85 (d, *J* = 4.6 Hz, 1H), 8.26-8.24 (m, 1H), 8.13-8.11 (m, 1H), 7.99 (s, 1H), 7.77-7.69 (m, 2H), 7.39 (d, *J* = 4.6 Hz, 1H), 5.00-4.94 (m, 1H), 4.13 (d, *J* = 3.3 Hz, 2H), 3.32 (t, *J* = 8.3 Hz, 1H), 3.06 (d, *J* = 9.5 Hz, 1H), 2.89-2.87 (m, 1H), 2.74-2.70 (m, 1H), 2.46-2.42 (m, 1H), 2.04 (t, *J* = 8.7 Hz, 1H), 1.48 (dd, *J* = 12.9, 7.1 Hz, 6H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 403.2).

EXAMPLE 68

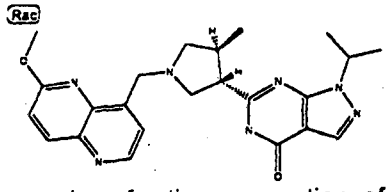
1-isopropyl-6-[(3S,4S)-4-methyl-1-(pyrido[2,3-b]pyrazin-8-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and pyrido[2,3-b]pyrazine-8-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.00 (brs, 1H), 9.16-9.10 (m, 3H), 8.00 (s, 1H), 7.78 (m, 1H), 5.00-4.97 (m, 1H), 4.63-4.58 (m, 1H), 4.34-4.18 (m, 1H), 3.30 (m, 1H), 3.27 (m, 1H), 2.92-2.77 (m, 2H), 2.49-2.38 (m, 1H), 2.09-1.97 (m, 1H), 1.48 (dd, *J* = 10.8, 6.6 Hz, 6H), 1.20 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 405.2).

EXAMPLE 69

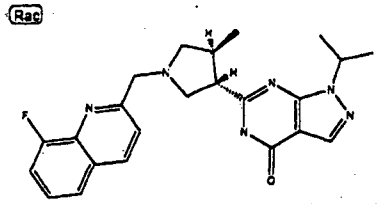
1-isopropyl-6-{(3,4-trans)-1-[(6-methoxy-1,5-naphthyridin-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 6-methoxy-1,5-naphthyridine-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.78 (d, *J* = 4.6 Hz, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 8.01 (s, 1H), 7.63 (m, 1H), 7.17 (d, *J* = 9.1 Hz, 1H), 5.01-4.95 (m, 1H), 4.4 (m, 1H), 4.07 (s, 3H), 3.48 (m, 1H), 3.18 (m, 1H), 2.89-2.75 (m, 2H), 2.43 (m, 1H), 2.10-2.08 (m, 2H), 1.49 (dd, *J* = 11.6, 6.6 Hz, 6H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 434.2).

EXAMPLE 70

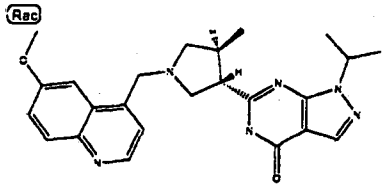
6-{(3,4-trans)-1-[(8-fluoroquinolin-2-yl)methyl]-4-methylpyrrolidin-3-yl}-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 8-fluoroquinoline-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.27-8.25 (m, 1H), 8.04 (s, 1H), 7.86 (m, 1H), 7.66-7.60 (m, 1H), 7.50-7.38 (m, 2H), 5.04-4.97 (m, 1H), 4.30 (m, 1H), 4.18 (m, 1H), 3.47 (m, 2H), 3.28 (m, 1H), 3.00 (m, 1H), 2.59 (m, 1H), 2.40 (m, 1H), 1.50 (dd, *J* = 11.2, 6.6 Hz, 6H), 1.22 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 421.2).

EXAMPLE 71

1-isopropyl-6-{(v)-1-[(6-methoxyquinolin-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

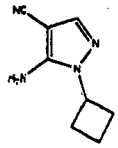


Following the procedure for the preparation of 1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-isopropyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one and 6-methoxyquinoline-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.87 (d, *J* = 5.0 Hz, 1H), 8.08 (d, *J* = 9.5 Hz, 1H), 8.00-7.95 (m, 2H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.61 (d, *J* = 2.9 Hz, 1H), 5.03-4.97 (m, 1H), 4.08 (s, 3H), 4.08-4.02 (m, 3H), 3.91-3.86 (m, 2H), 3.46-3.41 (m, 1H), 3.33 (s,

1H), 2.94 (m, 1H), 1.48 (d, *J* = 7.1 Hz, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 433.2).

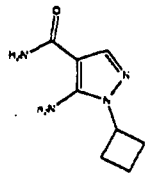
EXAMPLE 72

(a) 5-amino-1-cyclobutyl-1H-pyrazole-4-carbonitrile



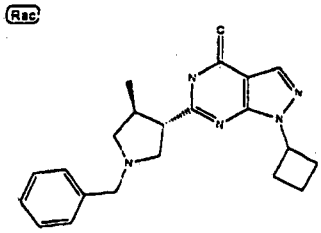
Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-cyclobutylhydrazine provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 1H), 4.48-4.40 (m, 1H), 4.23 (m, 2H), 2.70-2.58 (m, 2H), 2.48-2.35 (m, 2H), 1.97-1.79 (m, 2H). MS: (M+H m/z 163.1).

(b) 5-amino-1-cyclobutyl-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-cyclobutyl-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 7.71 (s, 1H), 4.71-4.55 (m, 1H), 2.61-2.50 (m,2H), 2.46-2.31 (m, 2H), 1.89-1.83 (m, 2H).

(c) 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclobutyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

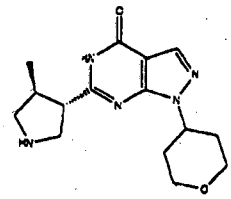


Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-

d]pyrimidin-4-one but substituting 5-amino-1-cyclobutyl-1H-pyrazole-4-carboxamide provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (d, *J* = 3.32 Hz, 1H), 7.35-7.24 (m, 5H), 5.25-5.20 (m, 1H), 3.79-3.57 (m, 3H), 3.36-3.32 (m, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.80-2.60 (m, 3H), 2.53-2.38 (m, 3H), 1.92-1.79 (m, 3H), 1.25-1.12 (m, 3H). MS: (M+H m/z 464.2).

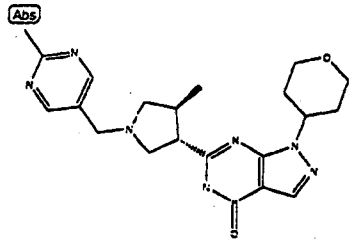
EXAMPLE 73

(a) 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (5.6g) was dissolved in 100 mL of methanol and added to a Parr bottle. Palladium hydroxide (3.76g) was added along with 3.56 mL of concentrated hydrochloric acid. The reaction mixture was placed on a hydrogenator under 40 psi of H2 for 18h. The reaction mixture was filtered through Celite and concentrated to provide 4.47g of the title compound as the hydrogen chloride salt. 400 MHz ^{1}H NMR (CD_3OD) δ 8.03 (s, 1H), 4.49 (m, 1H), 4.09-4.06 (m, 2H), 3.74-3.57 (m, 4H), 3.24 (m, 1H), 3.05 (m, 1H), 2.89 (m, 1H), 2.77 (m, 1H), 2.30 (m, 2H), 1.90 (m, 2H), 1.22 (d, *J* = 6.6 Hz, 3H). MS: (M^+H m/z = 304.2).

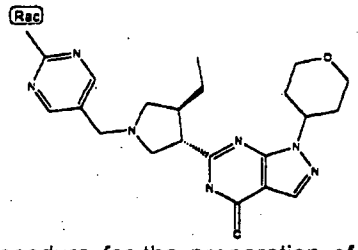
(b) 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride (493 mg) in 1,2-dichloroethane (10mL) was added acetic acid (174 mg), 2-methylpyrimidine-5-carbaldehyde (236 mg) and sodium triacetoxy borohydride (635 mg). The reaction mixture was heated at 50°C overnight. The reaction mixture was concentrated onto silica gel and purified by CombiFlash chromatography to provide the title compound (146 mg). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 2H), 8.01 (s, 1H), 4.82-4.76 (m, 1H), 4.12-4.08 (m, 2H), 3.68 (d, *J* = 5.0 Hz, 3H), 3.64-3.54 (m, 2H), 3.28 (t, *J* = 8.3 Hz, 1H), 3.04 (d, *J* = 9.9 Hz, 1H), 2.89-2.86 (m, 1H), 2.71 (s, 3H), 2.66-2.62 (m, 1H), 2.49-2.27 (m, 3H), 1.97 (t, *J* = 7.9 Hz, 1H), 1.91-1.83 (m, 2H), 1.19 (d, *J* = 7.05 Hz, 3H). MS: (M+H *m/z* 410.2).

EXAMPLE 74

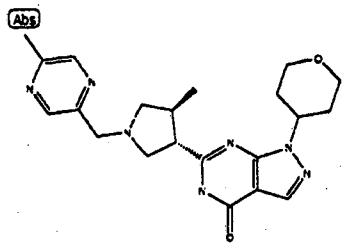
6-{(3,4-trans)-4-ethyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-[(3,4-trans)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.55 (brs, 1H), 8.64 (s, 2H), 8.01 (s, 1H), 4.81-4.73 (m, 1H), 4.11-4.09 (m, 2H), 3.68 (s, 2H), 3.61-3.53 (m, 2H), 3.28 (t, *J* = 8.7 Hz, 1H), 3.03 (d, *J* = 9.9 Hz, 1H), 2.94-2.92 (m, 1H), 2.71 (s, 3H), 2.57-2.53 (m, 1H), 2.40-2.20 (m, 3H), 1.96 (t, *J* = 8.7 Hz, 1H), 1.89-1.84 (m, 2H), 1.64-1.57 (m, 1H), 1.52-1.44 (m, 1H), 0.91 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 424.3).

EXAMPLE 75

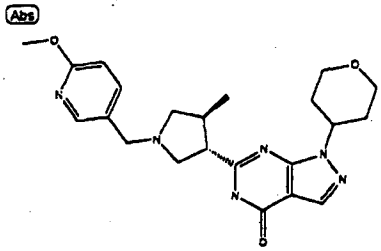
6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-methylpyrazine-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.47 (s, 1H), 8.03 (s, 1H), 4.83-4.79 (m, 1H), 4.12-4.03 (m, 2H), 3.78-3.75 (m, 1H), 3.61-3.55 (m, 2H), 3.46-3.40 (m, 1H), 3.12-3.09 (m, 1H), 2.87 (m, 1H), 2.64 (m, 1H), 2.53 (m, 2H), 2.47-2.28 (m, 4H), 2.16 (m, 2H), 1.91-1.84 (m, 2H), 1.23-1.20 (m, 3H). MS: (M+H m/z 410.3).

EXAMPLE 76

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

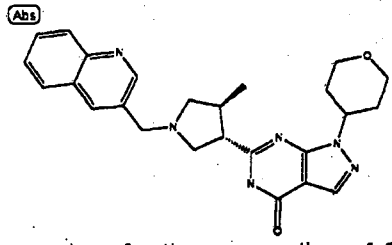


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (d, J = 2.1 Hz, 1H), 8.01 (s, 1H), 7.69 (dd, J = 8.7, 2.5 Hz,

1H), 7.77 (d, *J* = 8.7 Hz, 1H), 4.83-4.75 (m, 1H), 4.14-4.08 (m, 2H), 3.89 (s, 3H), 3.72-3.68 (m, 1H), 3.62-3.3.54 (m, 3H), 3.33 (t, *J* = 8.3 Hz, 1H), 2.99 (d, *J* = 9.9 Hz, 1H), 2.84-2.82 (m, 1H), 2.57-2.53 (m, 1H), 2.43-2.27 (m, 3H), 1.95-1.82 (m, 3H), 1.19 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 425.3).

EXAMPLE 77

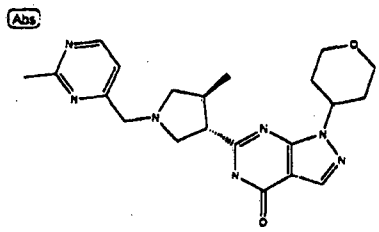
6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-3-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.86 (d, *J* = 2.1 Hz, 1H), 8.27 (d, *J* = 1.7 Hz, 1H), 8.08-8.06 (m, 1H), 8.03 (s, 1H), 7.90-7.57 (m, 1H), 7.70-7.66 (m, 1H), 7.56-7.52 (m, 1H), 4.83-4.75 (m, 1H), 4.11-4.07 (m, 2H), 4.02-3.99 (m, 1H), 3.85-3.82 (m, 1H), 3.60-3.53 (m, 2H), 3.33 (t, *J* = 8.3 Hz, 1H), 3.05 (d, *J* = 9.9 Hz, 1H), 2.87-2.85 (m, 1H), 2.68-2.60 (m, 1H), 2.53-2.40 (m, 1H), 2.38-2.29 (m, 2H), 2.05 (m, 1H), 1.90-1.84 (m, 2H), 1.19 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 445.1).

EXAMPLE 78

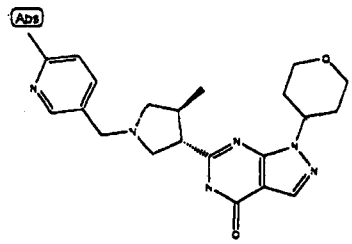
6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 2-methylpyrimidine-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.59 (d, J = 5.0 Hz, 1H), 8.03 (s, 1H), 7.20 (d, J = 5.0 Hz, 1H), 4.84-4.76 (m, 1H), 4.13-4.08 (m, 2H), 3.97-3.93 (m, 1H), 3.70-3.67 (m, 1H), 3.61-3.53 (m, 2H), 3.40 (t, J = 8.3 Hz, 1H), 3.14 (d, J = 9.5 Hz, 1H), 2.88 (m, 1H), 2.72 (s, 3H), 2.69-2.63 (m, 1H), 2.47-2.27 (m, 3H), 2.10-2.08 (m, 1H), 1.91-1.83 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 410.2).

EXAMPLE 79

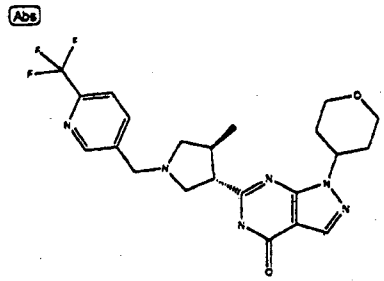
6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-methylnicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.38 (d, J = 2.1 Hz, 1H), 7.99 (s, 1H), 7.77 (d, J = 2.07 Hz, 1H), 7.75 (d, J = 2.07 Hz, 1H), 4.94-4.83 (m, 1H), 4.09-4.05 (m, 2H), 3.78-3.57 (m, 4H), 3.31-3.28 (m, 1H), 3.11-3.06 (m, 1H), 3.01-2.91 (m, 2H), 2.72-2.65 (m, 1H), 2.50 (s, 3H), 2.33-2.23 (m, 3H), 1.90-1.86 (m, 2H), 1.14 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 409.2).

EXAMPLE 80

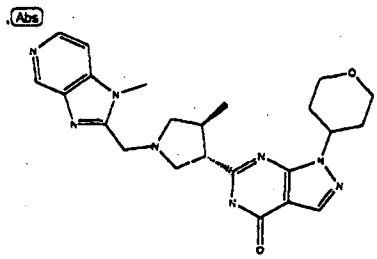
6-[(3S,4S)-4-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-(trifluoromethyl)nicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.64 (d, J = 1.7 Hz, 1H), 8.01 (s, 1H), 7.99 (d, J = 1.7 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 4.83-4.77 (m, 1H), 4.13-4.08 (m, 2H), 3.86-3.74 (m, 2H), 3.61-3.53 (m, 2H), 3.30 (t, J = 8.7 Hz, 1H), 3.03 (d, J = 9.9 Hz, 1H), 2.92-2.89 (m, 1H), 2.72-2.67 (m, 1H), 2.50-2.47 (m, 1H), 2.38-2.30 (m, 2H), 2.07-2.03 (m, 1H), 1.91-1.82 (m, 2H), 1.20 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 412.2).

EXAMPLE 81

6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

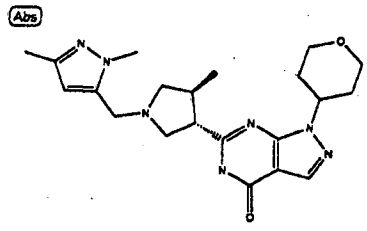


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-methyl-1H-imidazo[4,5-c]pyridine-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.83 (brs 1H), 9.01 (s, 1H), 8.41 (d, J = 15.8 Hz, 1H), 7.98

(s, 1H), 7.30 (d, J = 4.98 Hz, 1H), 4.79-4.75 (m, 1H), 4.13-4.06 (m, 3H), 4.00-3.96 (s, 4H), 3.60-3.52 (m, 2H), 3.30 (t, J = 8.7 Hz, 1H), 3.07 (d, J = 9.9 Hz, 1H), 2.92-2.89 (m, 1H), 2.82-2.77 (m, 1H), 2.48-2.45 (m, 1H), 2.36-2.27 (m, 2H), 2.19-2.17 (m, 1H), 1.89-1.79 (m, 2H), 1.23 (d, J = 6.6 Hz, 3H). MS: (M+H m/z 449.2).

EXAMPLE 82

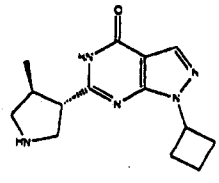
6-{(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1,3-dimethyl-1H-pyrazole-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 7.98 (s, 1H), 5.94 (s, 1H), 4.81-4.75 (m, 1H), 4.57 (s, 1H), 4.11-4.06 (m, 2H), 3.84 (s, 2H), 3.77 (s, 1H), 3.71-3.52 (m, 2H), 3.31 (t, J = 8.3 Hz, 1H), 3.01 (d, J = 9.9 Hz, 1H), 2.85-2.83 (m, 1H), 2.62-2.57 (m, 1H), 2.46-2.25 (m, 2H), 2.17-2.16 (m, 6H), 1.96-1.81 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H). MS: (M+H m/z 412.2).

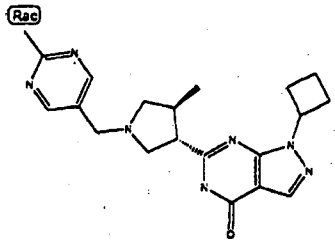
EXAMPLE 83

(a) 1-cyclobutyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclobutyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.03 (s, 1H), 5.39 (m, 1H), 3.79-3.38 (m, 4H), 3.08-2.71 (m, 4H), 2.43 (m, 2H),. 1.92 (m, 2H), 1.22 (m, 3H). MS: (M+H m/z 464.2).

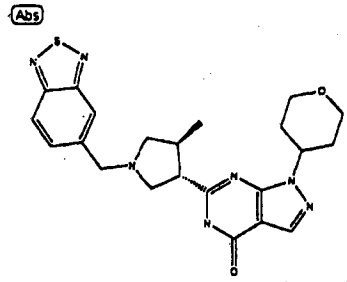
(b) 1-cyclobutyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 1-cyclobutyl-6-[(3,4-trans)-4-methylpyrrolidin-3-yl]-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.79 (brs, 1H), 8.63 (s, 2H), 8.04 (s, 1H), 5.28-5.22 (m, 1H), 3.68 (s, 2H), 3.24 (t, J = 8.3 Hz, 1H), 3.04 (d, J = 9.9 Hz, 1H), 2.89-2.87 (m, 1H), 2.80-2.67 (m, 5H), 2.51-2.38 (m, 3H), 2.03-1.81 (m, 4H), 1.18 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 480.2).

EXAMPLE 84

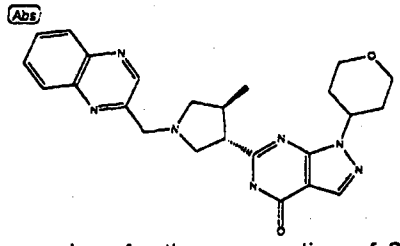
6-[(3S,4S)-1-(2,1,3-benzothiadiazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting benzo[c][1,2,5]thiadiazole-5-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.97 (brs, 1H), 8.02-8.00 (m, 2H), 7.86 (s, 1H), 7.77 (d, J = 1.2 Hz, 1H), 4.81-4.75 (m, 1H), 4.12-4.06 (m, 2H), 3.96-3.92 (m, 1H), 3.81-3.78 (m, 1H), 3.60-3.52 (m, 2H), 3.38 (t, J = 8.3 Hz, 1H), 3.03 (d, J = 9.9 Hz, 1H), 2.88-2.85 (m, 1H), 2.68-2.63 (m, 1H), 2.47-2.45 (m, 1H), 2.37-2.28 (m, 2H), 2.04 (t, J = 8.7 Hz, 1H), 1.90-1.80 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 452.1).

EXAMPLE 85

6-[(3S,4S)-4-methyl-1-(quinoxalin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

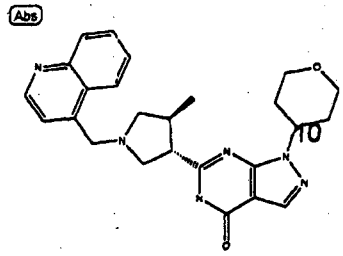


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoxaline-2-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 11.57 (brs, 1H), 8.89 (s, 1H), 8.26 (dd, J = 8.3, 1.2 Hz, 1H), 8.08-8.05 (m, 2H), 7.78-7.70 (m, 2H), 4.82 (m, 1H), 4.32-4.28 (m, 1H), 4.13-4.08 (m, 2H), 4.00-3.96 (m, 1H), 3.63-3.55 (m, 2H), 3.44 (t, J = 8.3 Hz, 1H), 3.26 (d, J =

9.9 Hz, 1H), 2.93-2.91 (m, 1H), 2.70-2.69 (m, 1H), 2.39-2.31 (m, 2H), 2.25-2.23 (m, 1H), 2.04 (s, 1H), 1.92-1.84 (m, 2H), 1.23 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 446.2).

EXAMPLE 86

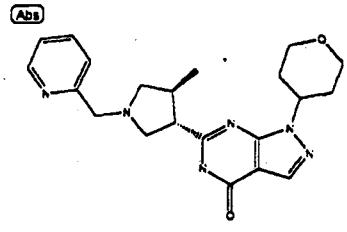
6-[(3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting quinoline-4-carbaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.68 (brs, 1H), 8.83 (d, *J* = 4.1 Hz, 1H), 8.25-8.22 (m, 1H), 8.12-8.08 (m, 1H), 7.98 (s, 1H), 7.75-7.72 (m, 1H), 7.54 (d, *J* = 3.3 Hz, 1H), 7.36 (d, *J* = 3.3 Hz, 1H), 5.21 (m, 1H), 4.77 (m, 1H), 4.13-4.06 (m, 3H), 3.59-3.52 (m, 2H), 3.32 (d, *J* = 8.7 Hz, 1H), 3.03 (d, *J* = 9.9 Hz, 1H), 2.88-2.86 (m, 1H), 2.72-2.69 (m, 1H), 2.36-2.28 (m, 3H), 2.04-2.00 (m, 1H), 1.89-1.84 (m, 2H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 445.1).

EXAMPLE 87

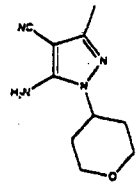
6-[(3S,4S)-4-methyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride (3.98g) in dimethylformamide (60 mL) was added 2-pyridyl carbaldehyde (1.63g) followed by acetic acid (1.34 mL) and sodium triacetoxy borohydride (4.99g). The reaction mixture was stirred for 20 minutes at ambient temperature and quenched with 24 mL of 1 N NaOH solution. The reaction mixture was adjusted to pH 9 with saturated sodium bicarbonate solution, extracted 3x with ethyl acetate and dried with magnesium sulfate, filtered and concentrated to give 3.6g of the title compound. The free base was dissolve in ethyl acetate and 25 mL of HCl/ethylacetate was added and stirred. The white solid was filtered and dried to provide 5.10g of the title compound as a dihydrogen chloride salt. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.64-8.63 (m, 1H), 8.03 (s, 1H), 7.72-7.67 (m, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.21-7.18 (m, 1H), 4.85-4.75 (m, 1H), 4.14-4.05 (m, 3H), 3.80-3.76 (m, 1H), 3.63-3.54 (m, 2H), 3.47-3.42 (m, 1H), 3.10 (m, 1H), 2.87 (m, 1H), 2.66 (m, 1H), 2.46-2.28 (m, 3H), 2.14 (m, 1H), 1.93-1.84 (m, 2H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 495.2).

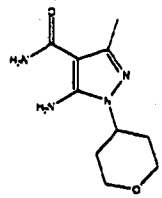
EXAMPLE 88

(a) 5-amino-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile



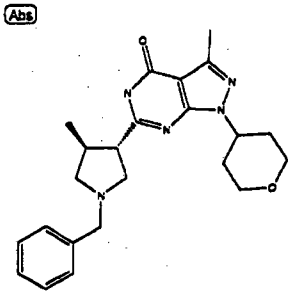
Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-(tetrahydro-2H-pyran-4-yl)hydrazine and 2-(1-methoxyethylidene) malononitrile provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 4.20 (m, 1H), 4.05 (m, 2H), 3.50 (m, 2H), 2.18 (s, 3H), 2.09 (m, 2H), 1.77 (m, 2H). MS: (M+H m/z 207.0).

(b) 5-amino-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4 carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 4.20 (m, 1H), 4.05 (m, 2H), 3.50 (m, 2H), 2.18 (s, 3H), 2.09 (m, 2H), 1.77 (m, 2H). MS: (M+H m/z 225.0).

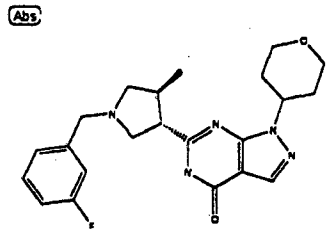
(c) 6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazole-4-carboxamide and (3S,4S)-methyl-1-benzyl-4-methylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.51-7.30 (m, 5H), 4.75-4.68 (m, 1H), 4.13-4.08 (m, 2H), 3.84-3.73 (m,1H), 3.63-3.48 (m, 2H), 3.40 (m,1H), 3.10-2.78 (m, 2H), 2.55 (s, 3H), 2.50-2.24 (m, 3H), 1.87-1.80 (m, 2H), .61-1.41 (m, 3H), 1.19 (d, J = 6.6 Hz, 3H). MS: (M^+H m/z = 408.1).

EXAMPLE 89

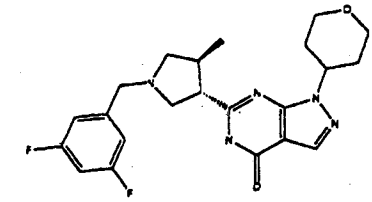
6-[(3S,4S)-1-(3-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 3-fluorobenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s,1H), 7.35-7.30 (m, 1H), 7.21-7.20 (m, 1H), 7.05 (d, *J* = 9.5 Hz, 1H), 6.98-6.93 (m, 1H), 4.83-4.77 (m, 1H), 4.14-4.08 (m, 2H), 3.80-3.77 (m, 1H), 3.64-3.54 (m, 3H), 3.36 (t, *J* = 8.8 Hz, 1H), 3.01 (d, *J* = 9.9 Hz, 1H), 2.84-2.83 (m, 1H), 2.57 (m, 1H), 2.44-2.27 (m, 3H), 1.95-1.83 (m, 3H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 412.4).

EXAMPLE 90

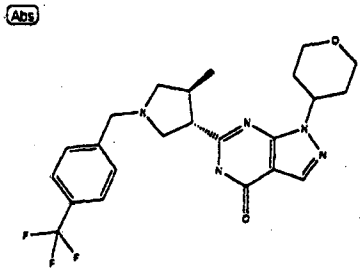
6-[(3S,4S)-1-(3,5-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 3,5-difluorobenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 6.93-6.90 (m, 2H), 6.73-6.69 (m, 1H), 4.81-4.80 (m, 1H), 4.14-4.10 (m, 2H), 3.79-3.67 (m, 2H), 3.62-3.55 (m, 2H), 3.30-3.26 (m, 1H), 3.10-3.07 (m, 1H), 2.95-2.92 (m, 1H), 2.83-2.79 (m, 1H), 2.26-2.53 (m, 1H), 2.38-2.32 (m, 2H), 2.18-2.14 (m, 1H), 1.91-1.85 (m, 2H), 1.18 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 430.4).

EXAMPLE 91

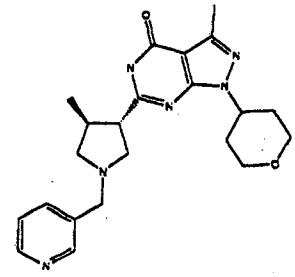
6-{(3S,4S)-4-methyl-1-[4-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 4-(trifluoromethyl)benzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.62-7.59 (m, 2H), 7.51-7.49 (m, 2H), 4.83-4.76 (m, 1H), 4.14-4.08 (m, 2H), 3.87-3.84 (m, 1H), 3.70-3.67 (m, 1H), 3.61-3.54 (m, 2H), 3.34 (t, *J* = 8.3 Hz, 1H), 3.01 (d, *J* = 9.9 Hz, 1H), 2.88-2.86 (m, 1H), 2.67-2.62 (m, 1H), 2.48-2.46 (m, 1H), 2.38-2.30 (m, 2H), 2.05-2.00 (m, 1H), 1.81-1.82 (m, 2H), 1.19 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 462.4).

EXAMPLE 92

3-methyl-6-[(3S,4S)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

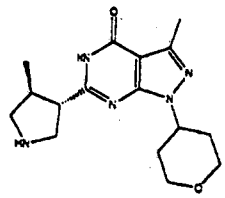


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 3-methyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-

d]pyrimidin-4(5H)-one and nicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.53 (m, 2H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.36-7.33 (m, 1H), 4.74-4.68 (m, 1H), 4.12-4.07 (m, 2H), 3.79-3.76 (m, 1H), 3.68-3.65 (m, 1H), 3.59-3.52 (m, 2H), 3.47 (s, 1H), 3.34 (t, *J* = 8.7 Hz, 1H), 2.99 (d, *J* = 9.9 Hz, 1H), 2.82-2.80 (m, 1H), 2.61-2.57 (m, 1H), 2.54 (s, 3H), 2.42-2.28 (m, 2H), 1.95 (t, *J* = 8.7 Hz, 1H), 1.87-1.78 (m, 2H), 1.19 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 409.2).

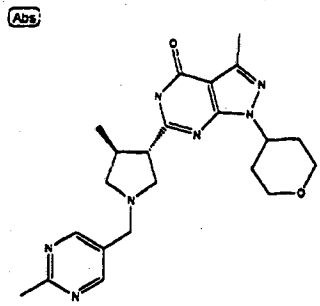
EXAMPLE 93

(a) 3-methyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 4.85-4.81 (m, 1H), 4.08-4.04 (m, 2H), 3.61-3.55 (m, 2H), 3.31-3.28 (m, 3H), 2.84-2.82 (m, 1H), 2.60-2.53 (m, 2H), 2.49 (s, 3H), 2.29-2.25 (m, 2H), 1.85-1.81 (m, 2H), 1.12 (d, *J* = 6.2 Hz, 3H). MS: (M^+H m/z = 249.1).

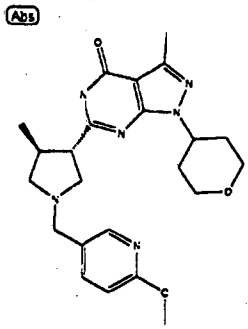
(b) 3-methyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 3-methyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 2H), 4.74-4.68 (m, 1H), 4.11-4.08 (m, 2H), 3.74-3.63 (m, 2H), 3.60-3.52 (m, 2H), 3.28 (t, *J* = 8.3 Hz, 1H), 3.03 (d, *J* = 9.5 Hz, 1H), 2.85-2.83 (m, 1H), 2.71 (s, 3H), 2.65-2.61 (m, 1H), 2.53 (s, 3H), 2.48-2.29 (m, 2H), 1.98 (t, *J* = 8.7 Hz, 1H), 1.87-1.80 (m, 3H), 1.19 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 424.2).

EXAMPLE 94

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

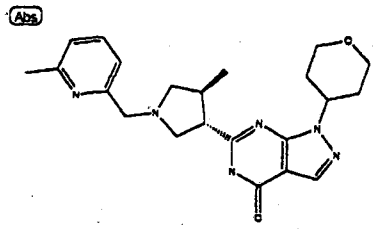


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 3-methyl-6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-

d]pyrimidin-4(5H)-one and 6-methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.03 (d, *J* = 2.1 Hz, 1H), 7.69 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 1H), 4.74-4.68 (m, 1H), 4.13-4.07 (m, 2H), 3.89 (s, 3H), 3.70-3.67 (m, 1H), 3.59-3.51 (m, 2H), 3.32 (t, *J* = 8.7 Hz, 1H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.79-2.77 (m, 1H), 2.54 (s, 3H), 2.53-2.50 (m, 1H), 2.41-2.29 (m, 2H), 1.92-1.78 (m, 3H), 1.30-1.18 (m, 2H), 10.86 (t, *J* = 76.6 Hz, 3H). MS: (M+H m/z 439.2).

EXAMPLE 95

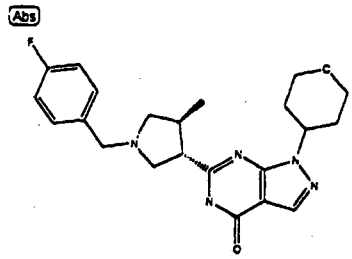
6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 6-methylpicolinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 4.83-4.77 (m, 1H), 4.13-4.08 (m, 2H), 3.99-3.95 (m, 1H), 3.72-3.69 (m, 1H), 3.62-3.54 (m, 2H), 3.42 (t, *J* = 8.3 Hz, 1H), 3.06 (d, *J* = 9.9 Hz, 1H), 2.85-2.83 (m, 1H), 2.64-2.57 (m, 1H), 2.55 (s, 3H), 2.44-2.29 (m, 3H), 2.08-2.03 (m, 1H), 1.91-1.82 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 409.1).

EXAMPLE 96

6-[(3S,4S)-1-(4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



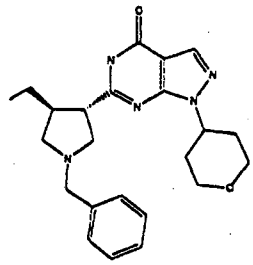
Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 4-fluorobenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.36-7.33 (m, 2H), 7.05-7.01 (m, 2H), 4.82-4.77 (m, 1H), 4.14-4.09 (m, 2H), 3.79-3.76 (m, 1H), 3.62-3.54 (m, 3H), 3.34 (t, *J* = 8.3 Hz, 1H), 2.99 (d, *J* = 9.9 Hz, 1H), 2.85-2.83 (m, 1H), 2.60-2.55 (m, 1H), 2.45-2.30 (m, 3H), 1.99-1.82 (m, 3H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 412.1).

EXAMPLE 97

(a) 6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting (3,4-trans)-ethyl 1-benzyl-4-methylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.40-7.26 (m, 5H), 4.78 (m, 1H), 4.12-4.09 (m, 2H), 3.82-3.804 (m, 1H), 3.65-3.54 (m, 3H), 3.35 (t, *J* = 8.3 Hz, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.89-2.86 (m, 1H), 2.48-2.32 (m, 3H), 2.20 (m, 1H), 1.95-1.87 (m, 2H), 1.63-1.58 (m, 2H), 1.50-1.49 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 408.1).

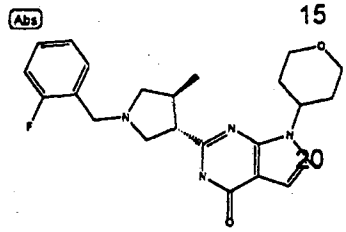
(b) 6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



The 6-[(3,4-trans)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one racemate was separated on Chiralcel OJ-H chiral HPLC column, Mobile Phase 80/20 CO_2/MeOH, T_R = 3.27, to provide the enantiomer. Analytical: AD column, Mobile Phase 85/15 Heptane/EtOH, T_R = 12.896. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.40-7.26 (m, 5H), 4.78 (m, 1H), 4.12-4.09 (m, 2H), 3.82-3.804 (m, 1H), 3.65-3.54 (m, 3H), 3.35 (t, *J* = 8.3 Hz, 1H), 2.98 (d, *J* = 9.9 Hz, 1H), 2.89-2.86 (m, 1H), 2.48-2.32 (m, 3H), 2.20 (m, 1H), 1.95-1.87 (m, 2H), 1.63-1.58 (m, 2H), 1.50-1.49 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 408.1).

EXAMPLE 98

6-[(3S,4S)-1-(2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

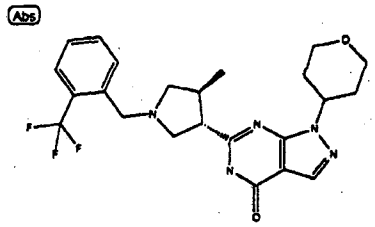


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 2-fluorobenzaldehyde provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 7.98 (s, 1H), 7.47-7.42 (m, 1H), 7.33-7.26 (m, 2H), 7.18-7.07 (m, 1H), 4.08-4.04 (m, 2H), 3.85 (s, 2H), 3.69-3.56 (m, 3H),

3.20-2.93 (m, 4H), 2.69-2.62 (m, 1H), 2.40-2.19 (m, 3H), 1.88-1.85 (m, 2H), 1.14 (d, J = 6.6 Hz, 3H). MS: (M+H m/z 412.1).

EXAMPLE 99

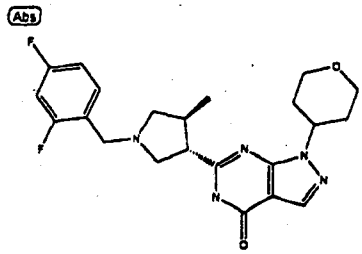
6-{(3S,4S)-4-methyl-1-[2-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 2-(trifluoromethyl)benzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 10.58 (brs, 1H), 8.01 (s, 1H), 7.79-7.76 (m, 1H), 7.64-7.58 (m, 2H), 7.37-7.34 (m, 1H), 4.83-4.76 (m, 1H), 4.14-4.08 (m, 2H), 3.88 (m, 2H), 3.62-3.54 (m, 2H), 3.39 (t, J = 8.3 Hz, 1H), 3.02-2.97 (m, 1H), 2.85 (m, 1H), 2.66 (m, 1H), 2.44-2.27 (m, 3H), 2.06-2.03 (m, 1H), 1.91-1.83 (m, 2H), 1.21 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 462.1).

EXAMPLE 100

6-[(3S,4S)-1-(2,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

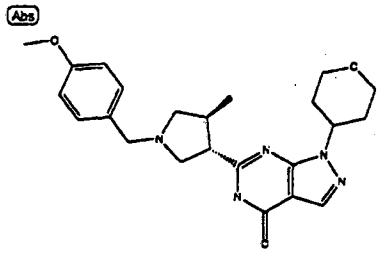


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 2,4-difluorobenzaldehyde provided the title compound.

400 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.40-7.38 (m, 2H), 6.90-6.79 (m, 2H), 4.81-4.77 (m, 2H), 4.14-4.08 (m, 2H), 3.88 (m, 2H), 3.62-3.54 (m, 2H), 3.32 (t, *J* = 8.7 Hz, 1H), 3.02 (d, *J* = 9.5 Hz, 1H), 2.86-2.83 (m, 1H), 2.65 (m, 1H), 2.43-2.20 (m, 3H), 2.00-1.83 (m, 2H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 430.2).

EXAMPLE 101

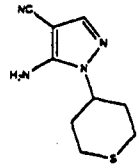
6-[(3S,4S)-1-(4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 4-methoxybenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.82-4.08 (m, 1H), 4.13-4.08 (m, 2H), 3.84-3.75 (m, 4H), 3.61-3.51 (m, 3H), 3.35 (t, *J* = 8.7 Hz, 1H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.82-2.80 (m, 1H), 2.53-2.49 (m, 1H), 2.42-2.30 (m, 3H), 1.95-1.82 (m, 3H), 1.18 (d, *J* = 7.1 Hz, 3H).

EXAMPLE 102

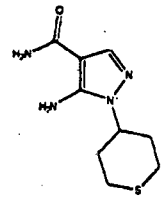
(a) 5-amino-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazole-4-carbonitrile



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carbonitrile but substituting 1-(tetrahydro-2H-thiopyran-4-yl)hydrazine provided the title compound. 400 MHz ^{1}H NMR

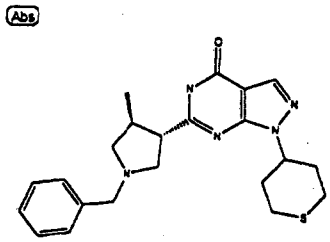
($CDCl_3$) δ 7.44 (s, 1H), 4.71 (s, 2H), 3.84-3.76 (m, 1H), 2.80-2.63 (m, 4H), 2.24-2.10 (m, 4H). MS: (M+H m/z 209.1).

(b) 5-amino-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazole-4-carboxamide



Following the procedure for the preparation of 5-amino-1-(2-methoxyphenyl)-1H-pyrazole-4-carboxamide but substituting 5-amino-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazole-4-carbonitrile provided the title compound. 400 MHz ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 4.09-3.97 (m, 1H), 2.89-2.82 (m, 2H), 2.72-2.68 (m, 2H), 2.15-2.10 (m, 4H). MS: (M+H m/z 227.1).

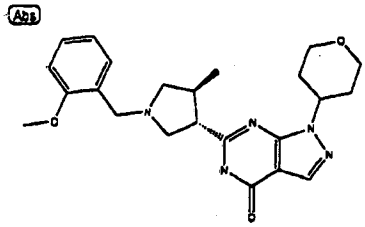
(c) 6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-thiopyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-[(3,4-trans)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(2-methoxyphenyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 5-amino-1-(tetrahydro-2H-thiopyran-4-yl)-1H-pyrazole-4-carboxamide and (3S,4S)-methyl-1-benzyl-4-methylpyrrolidine-3-carboxylate provided the title compound. 400 MHz ^1H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.41-7.26 (m, 5H), 4.60-4.53 (m, 1H), 3.86-3.83 (m, 1H), 3.65 (m, 1H), 3.41-3.37 (m, 1H), 3.02 (m, 1H), 2.94-2.75 (m, 4H), 2.60-2.31 (m, 3H), 2.25-2.16 (m, 2H), 1.99-1.94 (m, 1H), 1.62 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H). MS: (M+H m/z 410.2).

EXAMPLE 103

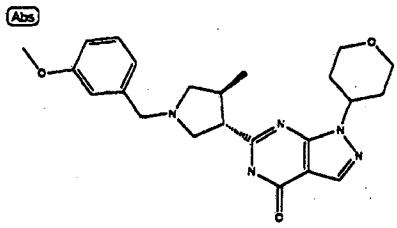
6-[(3S,4S)-1-(2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyano borohydride and 2-methoxybenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.29-7.22 (m, 2H), 6.92-6.88 (m, 2H), 4.83-4.75 (m, 1H), 4.14-4.08 (m, 2H), 3.93 (s, 3H), 3.76-3.69 (m, 2H), 3.62-3.54 (m, 2H), 3.34 (t, J = 8.7 Hz, 1H), 3.01 (d, J = 9.5 Hz, 1H), 2.78 (m, 1H), 2.56 (m, 1H), 2.41-2.27 (m, 3H), 1.92-1.82 (m, 3H), 1.18 (d, J = 7.1 Hz, 3H). MS: (M+H m/z 424.1).

EXAMPLE 104

6-[(3S,4S)-1-(3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

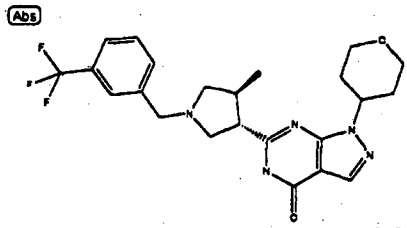


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 3-methoxybenzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.27-7.21 (m, 1H), 6.96-6.92 (m, 2H), 6.81 (d, J = 7.1 Hz, 1H), 4.82-4.76 (m, 1H), 4.14-4.08 (m, 2H), 3.85 (s,

3H), 3.79 (s, 1H), 3.62-3.54 (m, 3H), 3.39 (t, *J* = 8.7 Hz, 1H), 3.00 (d, *J* = 10.3 Hz, 1H), 2.81 (m, 1H), 2.53 (m, 1H), 2.42-2.28 (m, 3H), 1.94-1.82 (m, 3H), 1.20 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 424.1).

EXAMPLE 105

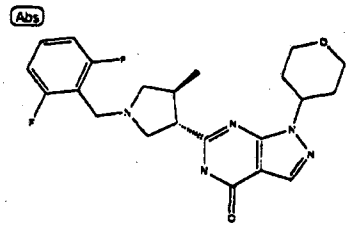
6-{(3S,4S)-4-methyl-1-[3-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 3-(trifluoromethyl)benzaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.68-7.63 (m, 1H), 7.55-7.51 (m, 3H), 4.84-4.76 (m, 1H), 4.14-4.08 (m, 2H), 3.87-3.84 (m, 1H), 3.71-3.69 (m, 1H), 3.62-3.54 (m, 2H), 3.36 (t, *J* = 8.3 Hz, 1H), 3.01 (m, 1H), 2.86 (m, 1H), 2.63-2.60 (m, 1H), 2.50-2.27 (m, 3H), 1.98-1.83 (m, 3H), 1.21 (d, *J* = 6.6 Hz, 3H). MS: (M+H m/z 462.1).

EXAMPLE 106

6-[(3S,4S)-1-(26-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

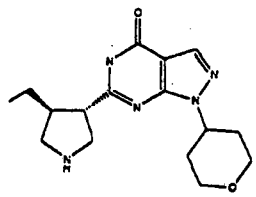


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting sodium cyanoborohydride and 2,6-difluorobenzaldehyde provided the title compound.

400 MHz ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.30-7.22 (m, 1H), 6.96-6.89 (m, 2H), 4.83-4.75 (m, 1H), 4.13-4.08 (m, 2H), 3.91 (s, 2H), 3.62-3.54 (m, 2H), 3.34 (t, *J* = 8.3 Hz, 1H), 3.06 (d, *J* = 9.5 Hz, 1H), 2.80 (m, 1H), 2.66 (m, 1H), 2.40-2.27 (m, 3H), 1.99 (m, 1H), 1.91-1.83 (m, 2H), 1.16 (d, *J* = 7.1 Hz, 3H). MS: (M+H m/z 430.1).

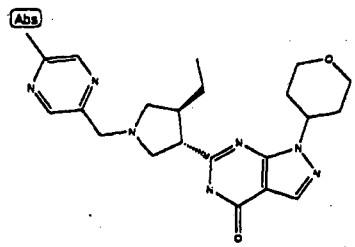
EXAMPLE 107

(a) 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one



Following the procedure for the preparation of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one but substituting 6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one provided the title compound. 400 MHz ^{1}H NMR (CD_3OD) δ 8.02 (s, 1H), 4.97 (m, 1H), 4.09-4.06 (m, 2H), 3.78-3.58 (m, 4H), 3.34-3.34 (m, 1H), 3.16-3.11 (m, 1H), 2.68 (d, *J* = 8.7 Hz, 1H), 2.63 (m, 1H), 2.32-2.27 (m, 2H), 1.90-1.87 (m, 2H), 1.69 (m, 1H), 1.57 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H). MS: (M+H m/z 318.2).

(b) 6-{(3S,4S)-4-ethyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

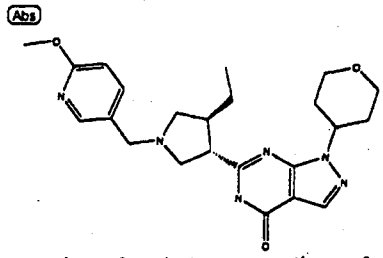


To a solution of 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one (4.4g) in

dimethylformamide (62 mL) was added acetic acid (2.4 mL), 5-methylpyrazine-2-carbaldehyde (2g) and sodium triacetoxyborohydride (5.27g). The reaction mixture stirred for 2h at ambient temperature and was carefully quenched with saturated sodium bicarbonate solution, extracted 3x with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via Biotage MPLC chromatography eluting with 1-4% methanol/methylene chloride/0.5 % saturated ammonium hydroxide provided the title compound (3.9g). 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.52-8.48 (m, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 4.81-4.75 (m, 1H), 4.11-4.01 (m, 3H), 3.79-3.75 (m, 1H) , 3.60-3.53 (m, 2H), 3.40-3.32 (m, 1H), 3.10-3.08 (m, 1H), 2.94 (m, 1H), 2.63-2.57 (m, 1H), 2.53 (d, *J* = 7.5 Hz, 1H), 2.37-2.18 (m, 4H), 1.90-1.83 (m, 2H), 1.67-1.60 (m, 1H), 1.54-1.47 (m, 1H), 0.95-0.92 (m, 3H). MS: (M+H m/z 424.2).

EXAMPLE 108

6-{(3S,4S)-4-ethyl-1-[(6-methoxypyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

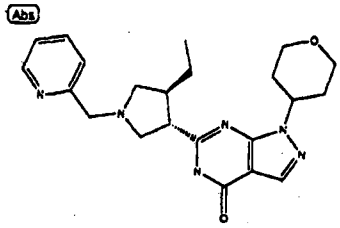


Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride, sodium cyanoborohydride and 6-methoxynicotinaldehyde provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 2.1 Hz, 1H), 8.02 (s, 1H), 7.73-7.71 (m, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 4.80-4.75 (m, 1H), 4.12-4.10 (m, 2H), 3.92-3.90 (m, 3H), 3.72-3.70 (m, 1H), 3.61-3.54 (m, 3H), 3.32 (t, *J* = 8.3 Hz, 1H), 2.99 (m, 1H), 2.91 (m, 1H), 2.41 (m, 1H), 2.40-2.28 (m, 2H), 2.21(m, 1H), 1.95 (m, 1H),

1.91-1.83 (m, 2H), 1.65-1.45 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H). MS: (M+H *m/z* 439.2).

EXAMPLE 109

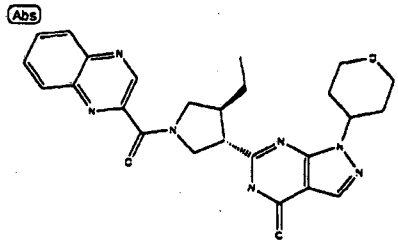
6-[(3S,4S)-4-ethyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride (51 mg) in acetonitrile (1 mL) was added potassium carbonate (88 mg) and 2-(bromomethyl)pyridine hydrogen bromide (40mg) and the reaction mixture was heated at reflux for 72 h in a sealed vial. The reaction mixture was concentrated onto silica and purified via CombiFlash flash chromatography to provide the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 11.50 (brs, 1H), 8.63 (dd, *J* = 1.7, 0.83, Hz, 1H), 8.02 (s, 1H), 7.70-7.67 (m, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.20-7.16 (m, 1H), 4.79-4.77 (m, 1H), 4.12-4.02 (m, 3H), 3.75-3.72 (m, 1H), 3.61-3.53 (m, 2H), 3.39 (t, *J* = 7.9 Hz, 1H), 3.07 (d, *J* = 9.9 Hz, 1H), 2.92-2.90 (m, 1H), 2.37-2.12 (m, 4H), 1.91-1.83 (m, 2H), 1.65-1.60 (m, 1H), 1.54-1.49 (m, 1H), 0.94 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 409.1).

EXAMPLE 110

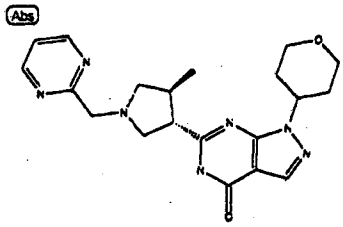
6-[(3S,4S)-4-ethyl-1-(quinoxalin-2-ylcarbonyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one



To a solution of 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride (73 mg) in dicloromethane (2 mL) was added triethylamine (62 mg) and 2-quinoxaloylchloride (40 mg) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 18h. The reaction mixture was quenched with saturated sodium bicarbonate, extracted with methylene chloride, dried with magnesium sulfate, filtered and concentrated. Purification via CombiFlash flash chromatography eluting with 2-4% MeOH/methylene chloride provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 12.78-12.62 (m, 1H), 9.41 (d, J = 7.5, Hz, 1H), 8.18-8.00 (m, 3H), 7.87-7.73 (m, 2H), 4.84-4.81 (m, 1H), 4.55-3.86 (m, 6H), 3.61-3.53 (m, 2H), 3.38-3.31 (m, 1H), 2.75 (m, 1H), 2.39-2.34 (m, 2H), 1.93-1.89 (m, 2H), 1.58-1.56 (m, 1H), 1.63-1.50 (m, 1H), 1.01-0.88 (m, 3H). MS: (M+H m/z 474.2).

EXAMPLE 111

6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one

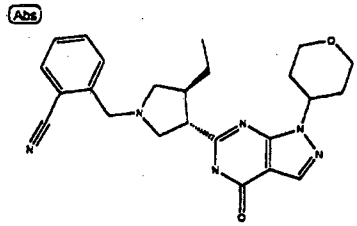


To a solution of 6-[(3S,4S)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride (7.75g) (see preparation in step (a) of Example 73) in dimethylformamide (115 mL) was added iron triflate (900 mg), 2-(chloromethyl)pyrimidine hydrogen chloride (4.5g), and cesium carbonate (22.2g) and the reaction mixture was heated at 60 °C for 24h. The reaction mixture was concentrated onto silica gel and purified by flash chromatography eluting with 0-15% methanol/ethyl acetate/1% saturated ammonium hydroxide to provide the title compound (6g). 400 MHz ^{1}H NMR ($CDCl_3$) δ 12.30 (brs, 1H), 8.63 (d, J = 5.0, Hz, 2H), 8.03 (s, 1H), 7.20 (d, J = 5.0, Hz, 1H), 4.84-4.79 (m, 1H), 4.30-4.27 (m, 1H),

4.14-4.08 (m, 2H), 3.87-3.82 (m, 1H), 3.63-3.55 (m, 2H), 3.47 (t, *J* = 7.9 Hz, 1H), 3.29 (d, *J* = 9.9 Hz, 1H), 2.88-2.86 (m, 1H), 2.60-2.56 (m, 1H), 2.46-2.24 (m, 4H), 1.93-1.84 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). MS: (M+H m/z 396.2).

EXAMPLE 112

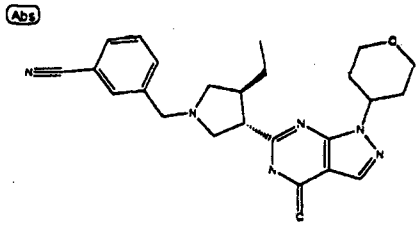
2-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-45-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride, sodium cyanoborohydride and 2-formylbenzonitrile provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 11.68 (brs, 1H), 8.01 (s, 1H), 7.68-7.58 (m, 3H), 7.40-7.36 (m, 1H), 4.91 (s, 1H), 4.82-4.76 (m, 1H), 4.12-4.10 (m, 2H), 3.94 (m, 1H), 3.61-6.55 (m, 2H), 3.37 (m, 1H), 3.03-2.94 (m, 2H), 2.66 (m, 1H), 2.41-2.23 (m, 3H), 2.09 (m, 1H), 1.91-1.84 (m, 2H), 1.66-1.49 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). MS: (M+H m/z 433.2).

EXAMPLE 113

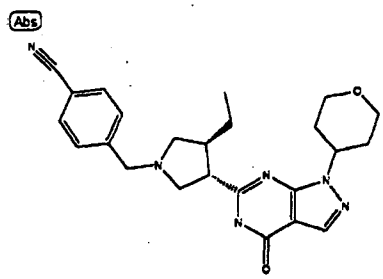
3-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride, sodium cyanoborohydride and 3-formylbenzonitrile provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.73-7.41 (m, 4H), 4.79 (m, 1H), 4.72 (s, 1H), 4.12-4.09 (m, 2H), 3.82-3.70 (m, 2H), 3.61-3.54 (m, 2H), 3.27 (t, *J* = 8.3 Hz, 1H), 3.02-2.97 (m, 2H), 2.71-2.70 (m, 1H), 2.37-2.30 (m, 2H), 2.20-2.14 (m, 1H), 1.90-1.87 (m, 2H), 1.61-1.60 (m, 1H), 1.51-1.49 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H). MS: (M+H m/z 433.2).

EXAMPLE 114

4-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-45-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile



Following the procedure for the preparation of 6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one but substituting 6-[(3S,4S)-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-one hydrogen chloride, sodium cyanoborohydride and 4-formylbenzonitrile provided the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ 11.82 (brs, 1H), 8.01 (s, 1H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.59-7.44 (m, 3H), 4.78-4.75 (m, 1H), 4.74 (s, 1H), 4.13-4.08 (m, 2H), 3.77 (m, 1H), 3.70 (m, 1H), 3.61-3.53 (m, 2H), 3.31-3.29 (m, 1H), 3.01-2.90 (m, 2H), 2.58 (m, 1H), 2.37-2.31 (m, 2H), 2.25 (m, 1H), 2.00 (m, 1H), 1.91-1.83 (m, 2H), 1.64-1.63 (m, 1H), 1.61-1.59 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H). MS: (M+H m/z 433.2).

BIOLOGICAL PROTOCOLS

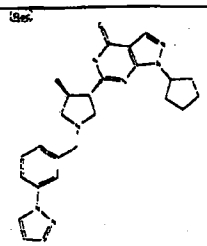
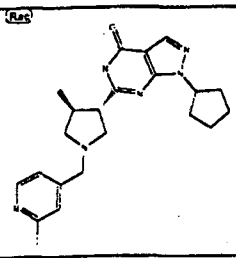
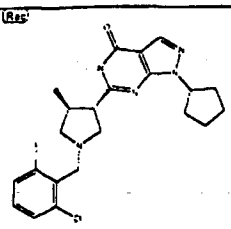
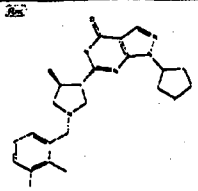
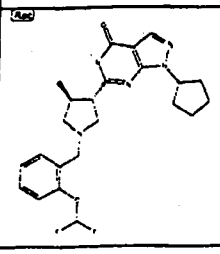
The utility of the compounds of Formula (I), and the pharmaceutically acceptable salts thereof, in the treatment or prevention of diseases (such as are detailed herein) in mammals (e.g., humans) may be demonstrated by the activity thereof in conventional assays known to one of ordinary skill in the art, including the assay described below. Such assays also provide a means whereby the activities of the compounds of Formula (I) can be compared with the activities of other known compounds.

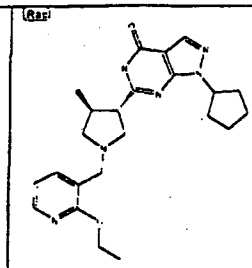
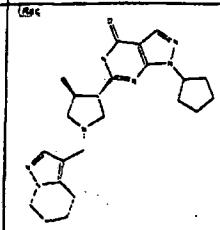
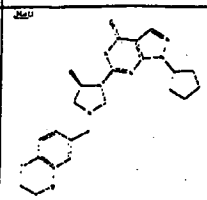
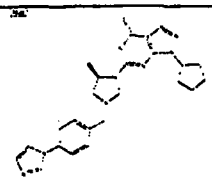
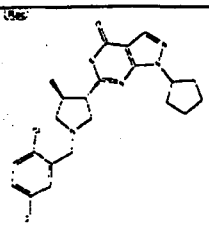
Phosphodiesterase 9 (PDE9) inhibitory activity

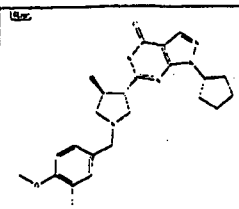
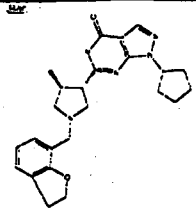
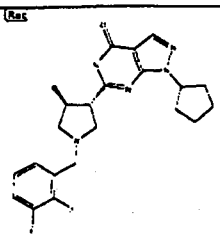
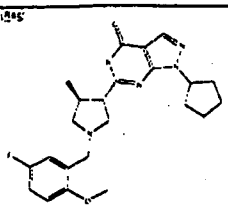
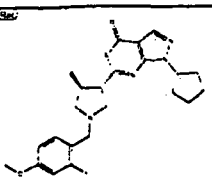
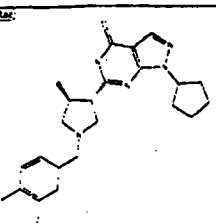
The PDE9 assay was performed using the Phosphodiesterase Scintillation Proximity (SPA) assay (GE Healthcare Life Sciences). The assay was carried out in 96 well clear bottom microtiter plates (Costar 3632, Corning Inc). The human recombinant PDE9 enzyme was generated in SF-9 cells, the cell pellets were sonicated in buffer (20 mM TRIS, 2mM benzamidine, 1mM EDTA, 250mM sucrose, 100µM PMSF, pH 7.5 with HCl), centrifuged at 40,000 x g for 20 min at 4°C. The supernatants were stored at -80°C. [8-^{3}H]guanosine 3',5'-cyclic phosphate (TRK 392, GE Healthcare Life Sciences) was diluted in assay buffer (50 mM Tris-HCl, pH7.5, containing 1.3 mM $MgCl_2$) such that the final well concentration was 50 nM. Test compounds were dissolved in DMSO, diluted in DI H_2O and serially diluted in 20%DMSO/80%H_2O, for a final concentration of 2% DMSO. For the assay the PDE9 was diluted with assay buffer such that 20% or less of the substrate was hydrolyzed to 5'GMP. Each assay well contained 10 µl of test compound or solvent, 40 µl of [^{3}H]cGMP and 50 µl of enzyme, background was determined by a high concentration of a PDE inhibitor. The assay was initiated with the addition of the enzyme and carried out at room temperature for 30 min. The assay was terminated with the addition of 10 µl of a PDE9 inhibitor that was sufficient to totally inhibit the enzyme activity, immediately followed by the addition of 50 µl per well of SPA beads. The plates were sealed, vortexed, allowed to set for >300 min, then counted in a Wallac TriLux MicroBeta LSC.

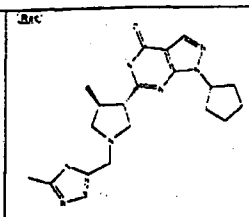
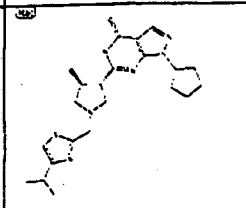
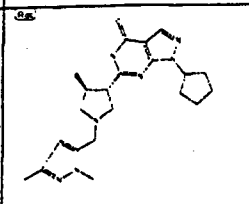
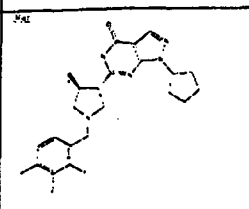
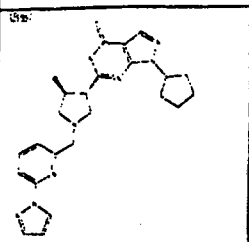
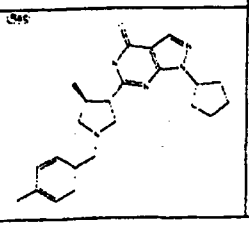
Example No.	G5678A (U):IC50	Example No.	G5678A (U):IC50	Example No.	G5678A (U):IC50
3	9.46 nM	43	36.4 nM	80	3.72 nM
4	624 nM	44	10.9 nM	81	2.92 nM
5	558 nM	45	38.7 nM	82	5.18 nM
6	57.1 nM	46	8.53 nM	83	24.5 nM
7	11.6 nM	47	5.53 nM	84	1.87 nM
8	11.2 nM	48	40.7 nM	85	0.903
9	2.84 nM	49	4.55 nM	86	1.44 nM
10	4.98 nM	50	125 nM	87	5.72 nM
11	18.9 nM	51	8.19 nM	88	17.9 nM
12	7.23 nM	52	26.0 nM	89	1.70 nM
13	6.61 nM	53	7.30 nM	90	1.41 nM
14	26.0 nM	54	14.7 nM	91	6.69 nM
17	16.2 nM	55	6.55 nM.	92	23.3 nM
18	8.26 nM	56	4.81 nM	93	24.3 nM
19	2.68 nM	57	122 nM	94	14.2 nM
20	7.06 nM	58	334 nM	95	3.92 nM
21	34.5 nM	59	7.37 nM	96	7.13 nM
22	43.6 nM	60	44.8 nM	97(a)	7.20 nM
23	1.32 nM	61	7.35 nM	97(b)	5.56 nM
24	119 nM	62	520 nM	98	7.93 nM
25	9.07 nM	63	123 nM	99	12.8 nM
26	11.4 nM	64	873 nM	100	22.7 nM
27	7.45 nM	65	17.1 nM	101	7.94 nM
28	6.86 nM	66	18.1 nM	102	19.7 nM
29	2.17 nM	67	9.74 nM	103	15.2 nM
31	23.2 nM	68	36.7 nM	104	3.98 nM
32	5.19 nM	69	30.7 nM	105	3.29 nM
33	6.29 nM	70	10.2 nM	106	8.06 nM
34	4.33 nM	71	16.1 nM	107	4.33 nM
35	53.8 nM	72	40.1 nM	108	3.11 nM
36	5.08 nM	73	6.01 nM	109	4.21 nM
37	3.23 nM	74	6.14 nM	110	2.59 nM
38	5.75 nM	75	5.46 nM	111	12.5 nM
39	58.1 nM	76	3.50 nM	112	1.37 nM
40	44.5 nM	77	1.24 nM	113	<1.00
41	63.8 nM	78	4.35 nM	114	2.31 nM
42	268 nM	79	3.72 nM		

The following additional compounds were made in accordance with the methods set forth above:

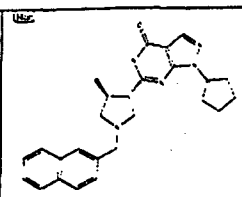
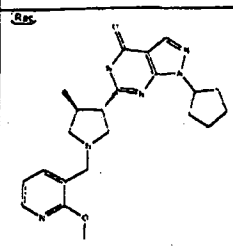
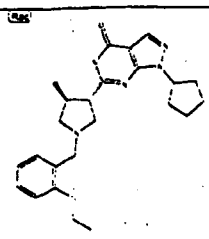
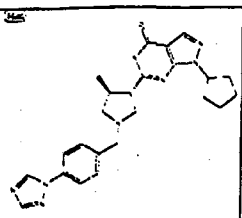
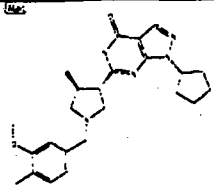
Ex. No.	Structure	IUPACNAME	G5678A (U):IC50	Exact Mass	Molec. Weight	Obs. *m/z* (M+1)	Retention Time
115		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[3-(1H-pyrazol-1-yl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	40.4 nM	443.243	557.579	444.28	2.71
116		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyridin-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	34.0 nM	392.233	620.556	393.32	2.04
117		6-[(3,4-trans)-1-(2-chloro-6-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	126 nM	429.173	543.951	430.23	2.7
118		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	74. nM	405.253	519.57	406.32	2.9
119		1-cyclopentyl-6-{(3,4-trans)-1-[2-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	32.8 nM	443.213	557.522	444.28	2.82

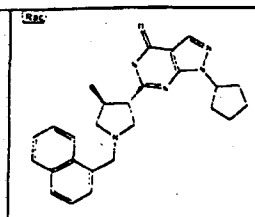
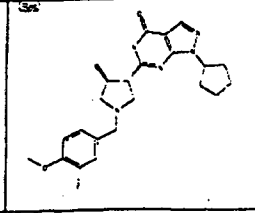
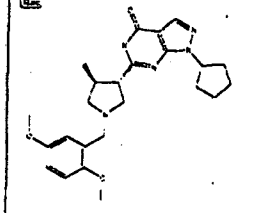
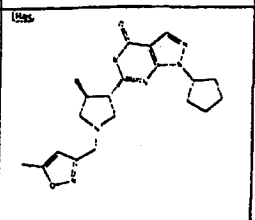
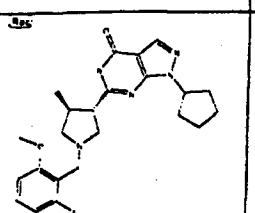
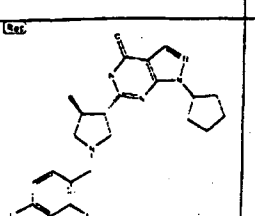
120		1-cyclopentyl-6-{(3,4-trans)-1-[(2-ethoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	62.7 nM	422.243	650.582	423.3	2.66
121		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	83.9 nM	421.259	535.573	422.33	2.43
122		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	56.4 nM	435.227	549.552	436.28	2.68
123		1-cyclopentyl-6-{(3,4-trans)-1-[4-(1H-imidazol-1-yl)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	39.3 nM	443.243	557.579	444.29	2.11
124		1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	80.9 nM	445.144	560.406	446.19	2.92

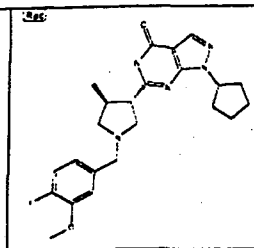
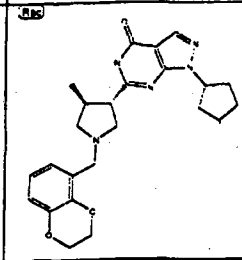
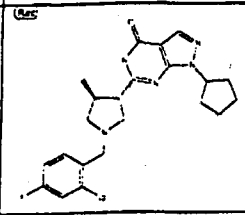
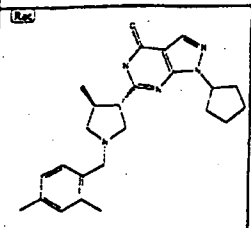
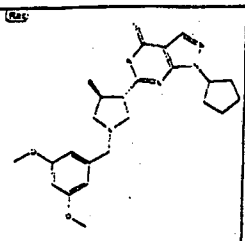
125		1-cyclopentyl-6-[(3,4-trans)-1-(4-methoxy-3-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	55.2 nM	421.248	535.569	422.31	2.89
126		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1-benzofuran-7-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	88.7 nM	419.232	533.553	420.31	2.75
127		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	61.7 nM	413.203	527.496	414.28	2.73
128		1-cyclopentyl-6-[(3,4-trans)-1-(5-fluoro-2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	70.9 nM	425.223	539.532	426.29	2.8
129		1-cyclopentyl-6-[(3,4-trans)-1-(2-fluoro-4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	71.8 nM	425.223	539.532	426.29	2.75
130		1-cyclopentyl-6-[(3,4-*trans*)-1-(3-fluoro-4-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	60.0 nM	409.228	523.533	410.28	2.87

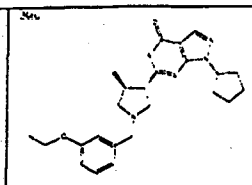
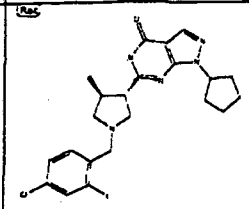
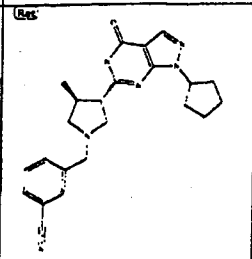
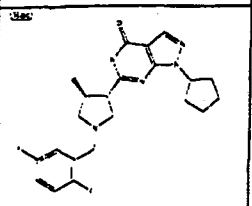
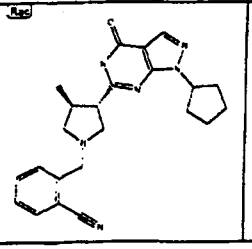
131		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methyl-1,3-thiazol-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	41.9 nM	398.189	512.557	399.23	2.32
132		1-cyclopentyl-6-{(3,4-trans)-1-[(4-isopropyl-1,3-thiazol-2-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	37.5 nM	426.22	540.611	427.28	2.83
133		1-cyclopentyl-6-{(3,4-trans)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	33.7 nM	395.243	509.535	396.31	2.35
134		1-cyclopentyl-6-{(3,4-trans)-1-(2,3-difluoro-4-methylbenzyl)-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	93.5 nM	427.218	541.523	428.29	2.89
135		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-{[6-(1H-pyrazol-1-yl)pyridin-2-yl]methyl}pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	91.6 nM	444.239	672.592	445.3	2.59
136		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	132 nM	391.237	505.543	392.31	2.81

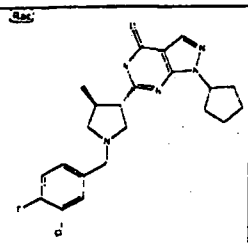
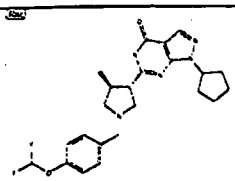
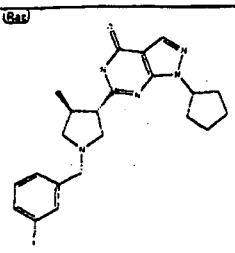
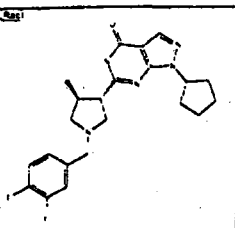
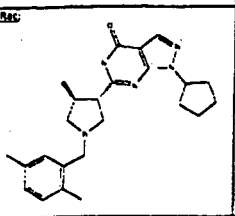
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137		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-naphthylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	54.5 nM	427.237	541.576	428.3	2.97
138		1-cyclopentyl-6-[(3,4-trans)-1-[(2-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	47.7 nM	408.227	636.555	409.29	2.5
139		1-cyclopentyl-6-[(3,4-trans)-1-(2-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	97.5 nM	421.248	535.569	422.33	2.88
140		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-[4-(1H-1,2,4-triazol-1-yl)benzyl]pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	26.8 nM	444.239	558.567	445.3	2.42
141		1-cyclopentyl-6-[(3,4-trans)-1-(3-methoxy-4-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	53.1 nM	421.248	535.569	422.3	2.94

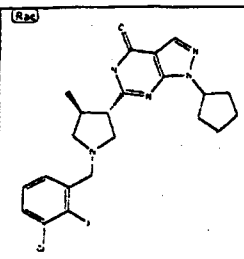
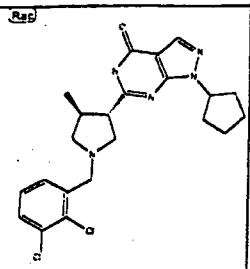
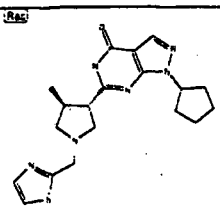
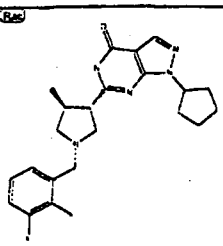
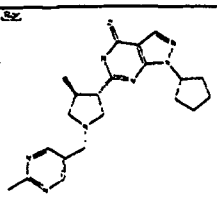
142		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(1-naphthylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	47.5 nM	427.237	541.576	428.3	2.93
143		1-cyclopentyl-6-[(3,4-trans)-1-(3-fluoro-4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	35.1 nM	425.223	539.532	426.29	2.73
144		1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	89.6 nM	437.243	551.568	438.29	2.79
145		1-cyclopentyl-6-((3,4-trans)-4-methyl-1-[(5-methylisoxazol-3-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	77.4 nM	382.212	496.492	383.27	2.5
146		1-cyclopentyl-6-[(3,4-trans)-1-(2-fluoro-6-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	165 nM	425.223	539.532	426.29	2.76
147		1-cyclopentyl-6-[(3,4-trans)-1-(2,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	79.8 nM	413.203	527.496	414.28	2.72

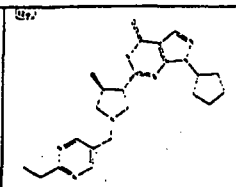
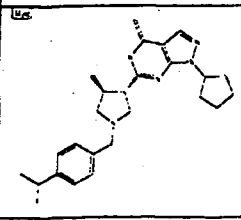
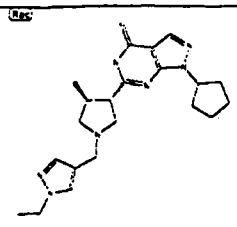
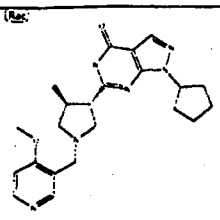
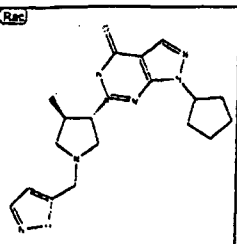
148		1-cyclopentyl-6-[(3,4-trans)-1-(4-fluoro-3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	36.0 nM	425.223	539.532	426.29	2.79
149		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	47.1 nM	435.227	549.552	436.28	2.73
150		6-[(3,4-trans)-1-(2-chloro-4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-]pyrimidin-4-one	83.5 nM	429.173	543.951	430.23	2.82
151		1-cyclopentyl-6-[(3,4-trans)-1-(2,4-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	117 nM	405.253	519.57	406.32	2.92
152		1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	42.2 nM	437.243	551.568	438.29	2.8

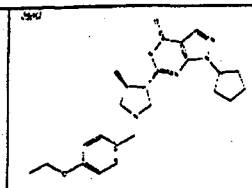
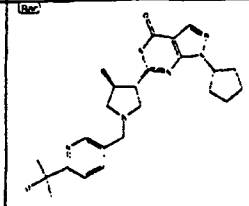
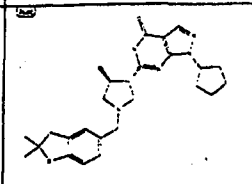
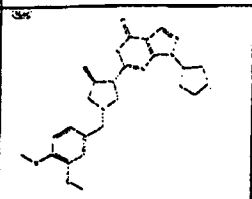
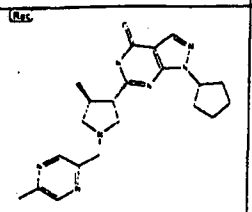
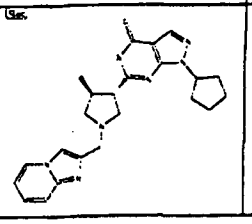
153		1-cyclopentyl-6-[(3,4-trans)-1-(3-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	54.4 nM	421.248	535.569	422.28	2.88
154		6-[(3,4-trans)-1-(4-chloro-2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	175 nM	429.173	543.951	430.23	2.88
155		3-[[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl]benzonitrile	27.9 nM	402.217	516.526	403.25	2.61
156		1-cyclopentyl-6-[(3,4-trans)-1-(2,5-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	40.8 nM	413.203	527.496	414.27	2.69
157		2-[[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl]benzonitrile	56.4 nM	402.217	516.526	403.26	2.6

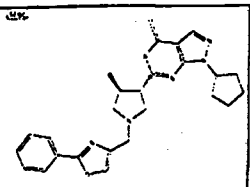
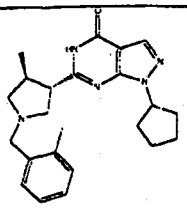
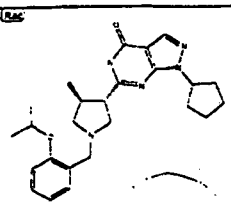
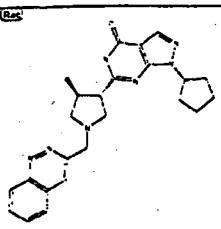
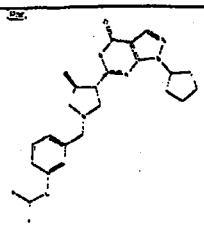
158		6-[(3,4-trans)-1-(3-chloro-4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	50.9 nM	429.173	543.951	430.21	2.91
159		1-cyclopentyl-6-((3,4-trans)-1-[4-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	59.9 nM	443.213	557.522	444.26	2.88
160		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(3-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	43.4 nM	391.237	505.543	392.29	2.8
161		1-cyclopentyl-6-[(3,4-trans)-1-(3,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	40.4 nM	413.203	527.496	414.26	2.8
162		1-cyclopentyl-6-[(3,4-trans)-1-(2,5-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	60.1 nM	405.253	519.57	406.32	2.92

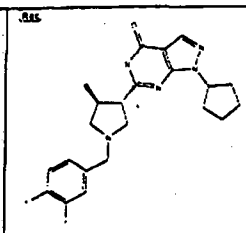
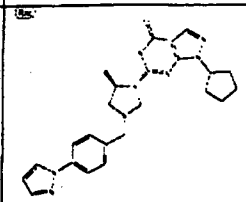
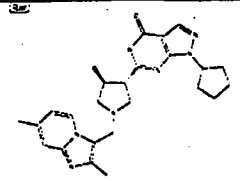
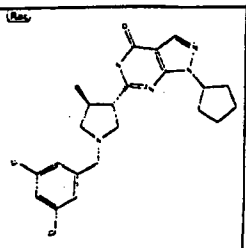
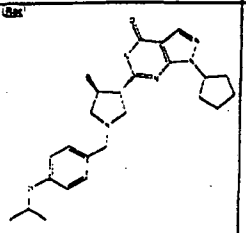
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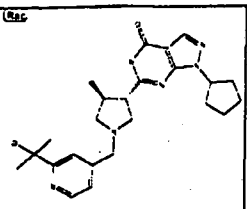
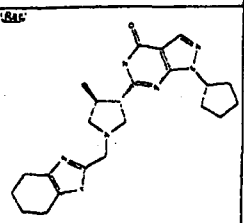
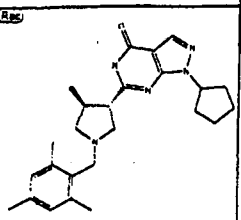
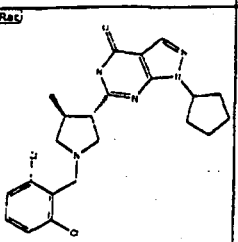
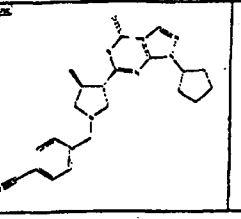
163		6-[(3,4-trans)-1-(3-chloro-2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	53.4 nM	429.173	543.951	430.22	2.85
164		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	78.9 nM	445.144	560.406	446.15	2.94
165		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(1,3-thiazol-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	54.2 nM	384.173	498.53	385.22	2.35
166		1-cyclopentyl-6-[(3,4-trans)-1-(3-fluoro-2-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	68.3 nM	409.228	523.533	410.26	2.83
167		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	40.7 nM	393.228	507.519	394.3	2.21

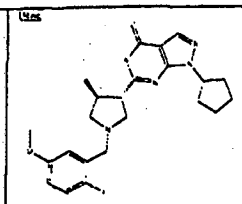
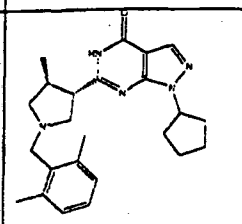
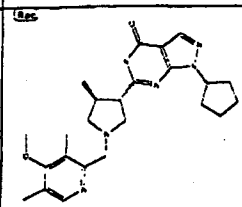
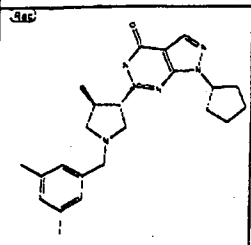
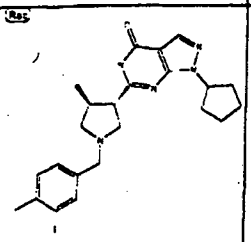
168		1-cyclopentyl-6-{(3,4-trans)-1-[(2-ethylpyrimidin-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	30.7 nM	407.243	521.546	408.31	2.36
169		1-cyclopentyl-6-{(3,4-trans)-1-(4-isopropylbenzyl)-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	117 nM	419.269	533.597	420.34	3.1
170		1-cyclopentyl-6-{(3,4-trans)-1-[(1-ethyl-1H-pyrazol-4-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	74.6 nM	395.243	509.535	396.31	2.37
171		1-cyclopentyl-6-{(3,4-trans)-1-[(4-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	51.3 nM	408.227	636.555	409.29	2.05
172		1-cyclopentyl-6-{(3,4-trans)-1-(isoxazol-5-ylmethyl)-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	67.0 nM	368.196	482.465	369.25	2.29

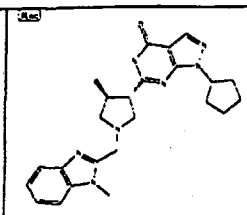
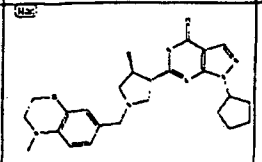
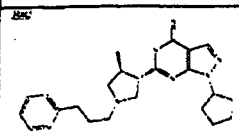
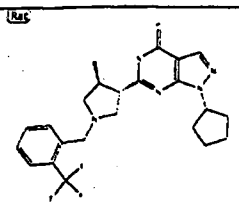
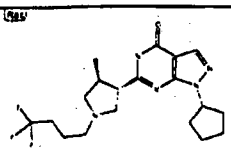
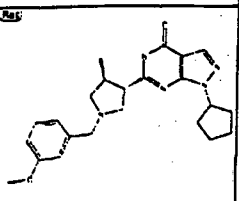
173		1-cyclopentyl-6-[(3,4-trans)-1-(4-ethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	64.0 nM	421.248	535.569	422.29	2.85
174		1-cyclopentyl-6-[(3,4-trans)-1-{[6-(1-hydroxy-1-methylethyl)pyridin-3-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	42.0 nM	436.259	664.609	437.32	2.14
175		1-cyclopentyl-6-{(3,4-trans)-1-[(2,2-dimethyl-2,3-dihydro-1-benzofuran-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	74.8 nM	447.264	561.607	448.3	2.96
176		1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	27.1 nM	437.243	551.568	438.29	2.59
177		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	42.2 nM	393.228	507.519	394.3	2.32
178		1-cyclopentyl-6-[(3,4-trans)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	44.7 nM	417.228	531.541	418.27	2.14

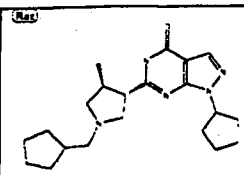
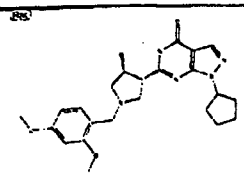
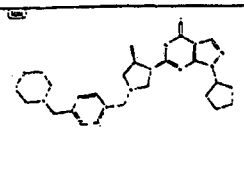
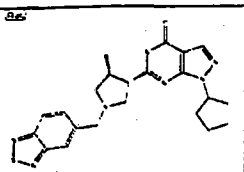
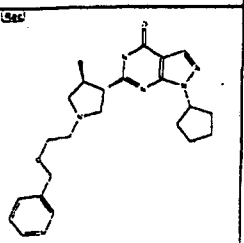
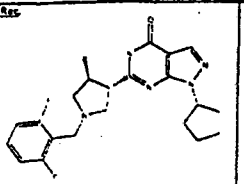
179		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-phenyl-1,3-oxazol-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	47.2 nM	444.227	558.563	445.27	2.88
180		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(2-methylbenzyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	83.8 nM	391.237	505.543	392.3	2.77
181		1-cyclopentyl-6-[(3,4-trans)-1-(2-isopropoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	134 nM	435.264	549.596	436.33	3
182		6-[(3,4-trans)-1-(cinnolin-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	22.5 nM	429.228	543.552	430.26	2.53
183		1-cyclopentyl-6-{(3,4-trans)-1-[3-(difluoromethoxy)benzyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	29.8 nM	443.213	557.522	444.26	2.87

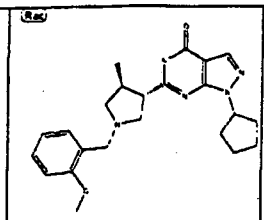
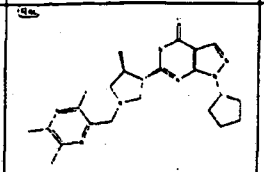
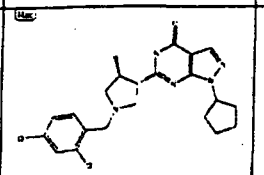
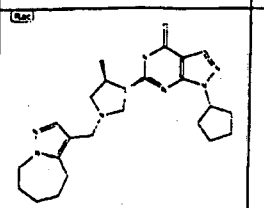
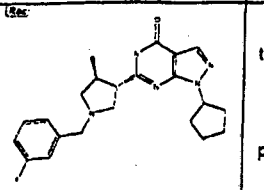
184		1-cyclopentyl-6-[(3,4-trans)-1-(4-fluoro-3-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	90.0 nM	409.228	523.533	410.26	2.87
185		1-cyclopentyl-6-((3,4-trans)-4-methyl-1-[4-(1H-pyrazol-1-yl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	33.5 nM	443.243	557.579	444.27	2.69
186		1-cyclopentyl-6-{(3,4-trans)-1-[(2,7-dimethylimidazo[1,2-a]pyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	155 nM	445.259	559.595	446.27	2.19
187		1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	70.9 nM	445.144	560.406	446.16	3.04
188		1-cyclopentyl-6-[(3,4-trans)-1-(4-isopropoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	72.7 nM	435.264	549.596	436.3	2.98

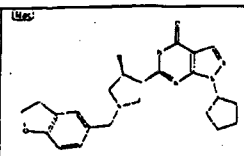
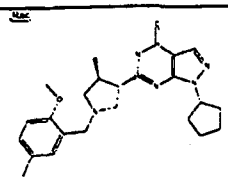
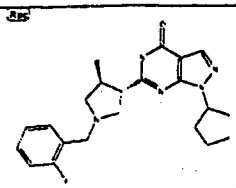
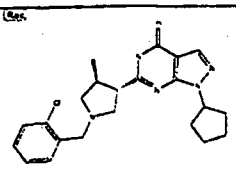
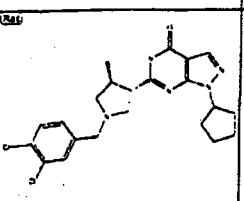
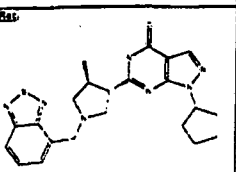
189		1-cyclopentyl-6-[(3,4-trans)-1-{[2-(1-hydroxy-1-methylethyl)pyridin-4-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	23.7 nM	436.259	664.609	437.21	2.13
190		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	55.4 nM	438.22	552.622	439.27	2.81
191		1-cyclopentyl-6-[(3,4-trans)-1-(mesitylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	198 nM	419.269	533.597	420.34	3
192		1-cyclopentyl-6-[(3,4-trans)-1-(2,6-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	236 nM	445.144	560.406	446.14	2.75
193		4-{[(3,4-trans)-3-(1-cyclopentyl-4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-4-methylpyrrolidin-1-yl]methyl}benzonitrile	57.7 nM	402.217	516.526	403.25	2.61

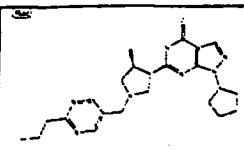
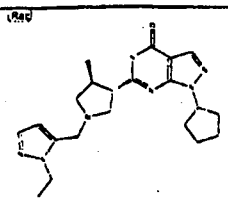
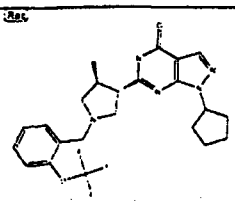
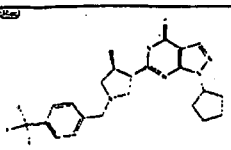
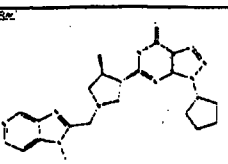
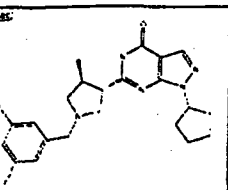
194		1-cyclopentyl-6-[(3,4-*trans*)-1-(2-*fluoro*-5-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	54.7 nM	425.223	539.532	426.29	2.75
195		1-cyclopentyl-6-[(3,4-trans)-1-(2,6-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	198 nM	405.253	519.57	406.31	2.83
196		1-cyclopentyl-6-[(3,4-trans)-1-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	187 nM	436.259	664.609	437.32	2.76
197		1-cyclopentyl-6-[(3,4-trans)-1-(3,5-dimethylbenzyl)-4-*methylpyrrolidin*-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	53.5 nM	405.253	519.57	406.33	2.96
198		1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dimethylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	93.6 nM	405.253	519.57	406.31	2.94

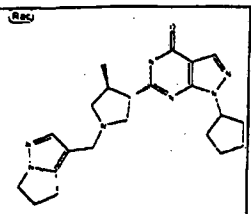
199		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	35.3 nM	431.243	545.568	432.29	2.64
200		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	176 nM	448.259	676.62	(449.3)	(2.78)
201		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(3-phenylpropyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	146 nM	405.253	519.57	(406.3)	(2.93)
202		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[2-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	104 nM	445.209	559.513	(446.2)	(2.9)
203		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(4,4,4-trifluorobutyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	83.7 nM	397.209	511.469	(398.2)	(2.69)
204		1-cyclopentyl-6-[(3,4-trans)-1-(3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	9.56 nM	407.232	521.542	(408.3)	(2.74)

205		1-cyclopentyl-6-[(3,4-trans)-1-(cyclopentylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	286 nM	369.253	483.537	{370.2}	{2.72}
206		1-cyclopentyl-6-[(3,4-trans)-1-(2,4-dimethoxybenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	68.4 nM	437.243	551.568	{438.2}	{2.82}
207		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(morpholin-4-ylmethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	46.2 nM	476.29	590.649	{477.3; 477.3}	{1.94;2.17}
208		6-[(3,4-trans)-1-(2,1,3-benzothiadiazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	7.13 nM	435.184	549.578	{436.2}	{2.66}
209		6-{(3,4-trans)-1-[2-(benzyloxy)ethyl]-4-methylpyrrolidin-3-yl}-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	52.9 nM	421.248	535.569	{422.2}	{2.85}
210		1-cyclopentyl-6-[(3,4-trans)-1-(2,6-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	16.2 nM	413.203	527.496	{414.2}	{2.62}

211		1-cyclopentyl-6-{(3,4-trans)-1-(2-methoxybenzyl)-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	39.8 nM	407.232	521.542	{408.2}	{2.76}
212		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(3,5,6-trimethylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	9.98 nM	421.259	535.573	{422.3}	{2.51}
213		1-cyclopentyl-6-{(3,4-trans)-1-(2,4-dichlorobenzyl)-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	124 nM	445.144	560.406	{446.1}	{2.98}
214		1-cyclopentyl-6-[(3,4-trans)-4-methyl-1-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	15.7 nM	435.275	549.6	{436.3}	{2.59}
215		1-cyclopentyl-6-[(3,4-trans)-1-(3-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	11.5 nM	395.212	509.506	{396.2}	{2.73}

216		1-cyclopentyl-6-[(3,4-trans)-1-(2,3-dihydro-1-benzofuran-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	17.4 nM	419.232	533.553	(420.2)	(2.71)
217		1-cyclopentyl-6-[(3,4-trans)-1-(2-methoxy-5-methylbenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	25.0 nM	421.248	535.569	(422.3)	(2.91)
218		1-cyclopentyl-6-[(3,4-trans)-1-(2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	15.6 nM	395.212	509.506	(396.2)	(2.67)
219		6-[(3,4-trans)-1-(2-chlorobenzyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	48.4 nM	411.183	525.961	(412.2)	(2.78)
220		1-cyclopentyl-6-[(3,4-trans)-1-(3,4-dichlorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	28.0 nM	445.144	560.406	(446.1)	(3.04)
221		6-[(3,4-trans)-1-(2,1,3-benzothiadiazol-4-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	12.7 nM	435.184	549.578	(436.2)	(2.67)

222		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(2-propylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	6.03 nM	421.259	535.573	(422.3)	(2.52)
223		1-cyclopentyl-6-{(3,4-trans)-1-[(1-ethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	14.4 nM	395.243	509.535	(396.3)	(2.39)
224		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[2-(trifluoromethoxy)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	116 nM	461.204	575.512	(462.2)	(2.96)
225		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[4-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	34.9 nM	445.209	559.513	(446.2)	(3.01)
226		1-cyclopentyl-6-{(3,4-trans)-4-methyl-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	3.78 nM	432.239	660.581	(433.2)	(2.03)
227		1-cyclopentyl-6-[(3,4-trans)-1-(3,5-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	7.42 nM	413.203	527.498	(414.2)	(2.79)

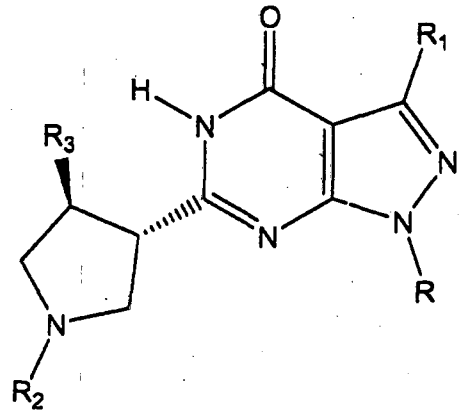
228		1-cyclopentyl-6-[(3,4-trans)-1-(5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one	49.1 nM	407.243	521.546	{408.3}	{2.37}

Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention. Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

CLAIMS

We claim:

1. A compound of Formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, each of which optionally may be substituted with one to three substituents, the substituents being independently selected from the group consisting of $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo, and $(C_1\text{-}C_4)$haloalkyl.

R_1 is selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_1\text{-}C_4)$haloalkyl, and cyclopropyl;

R_2 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$haloalkyl, heteroaryl selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, and ER_5, wherein the heteroaryl optionally may be substituted with one to three substituents independently selected from the group consisting of $(C_1\text{-}C_4)$alkyl and $(C_1\text{-}C_4)$haloalkyl;

R_3 is selected from the group consisting of hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, and $(C_1\text{-}C_4)$haloalkyl;

E is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, and $-C(O)-$;

R_5 is selected from the group consisting of (C_3-C_8)cycloalkyl, heterocycloalkyl, aryl, aryloxy, and heteroaryl, any of which optionally may be substituted with one to three substituents, such substituents being independently selected from the group consisting of (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_1-C_4)hydroxyalkyl, (C_1-C_4)haloalkyl, (C_1-C_4)alkoxy, (C_1-C_4)haloalkoxy, (C_3-C_8)cycloalkyl, halo, cyano, phenyl, morpholinyl, (C_1-C_4)alkylamino, pyrazolyl, triazolyl, and imidazolyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of ethyl, isopropyl, trifluoroethyl, cyclobutyl, cyclopentyl, difluorocyclohexyl, methoxyphenyl, tetrahydro-2H-thiopyran-4-yl, and tetrahydro-2H-pyran-4-yl;

R_1 is hydrogen or methyl;

R_2 is methyl, trifluoroethyl, trifluorobutyl, pyrimidinyl, trifluoromethylpyrimidinyl, or ER_5;

R_3 is methyl, ethyl, isopropyl, trifluoromethyl, trifluoroethyl, or cyclopropyl;

E is $-CH_2-$ or $-C(O)-$;

R_5 is selected from the group consisting of substituted or unsubstituted cyclopentyl, morpholinyl, phenyl, naphthyl, benzyloxy, pyrimidinyl, pyridinyl, quinolinyl, quinoxalinyl, pyrazinyl, pyrazolyl, benzimidazolyl, cinnolinyl, naphthydrinyl, pyrido[2,3-b]pyrazinyl, imidazo[4,5-c]pyridinyl, benzothiadiazolyl, tetrahydropyrazolo[1,5-a]pyridinyl, dihydrobenzodioxinyl, imidazolyl, dihydrobenzofuranyl, triazolyl, oxazolyl, isoxazolyl, benzodioxinyl, thiazolyl, imidazo[1,2-a]pyridinyl, tetrahydrobenzothiazolyl, dihydrobenzoxazinyl, tetrahydropyranyl, tetrahydropyrazolo[1,5-a]azepinyl, and dihydropyrrolo[1,2-b]pyrazolyl.

3. The compound of claim 2, or a pharmaceutically acceptable salt thereof, wherein:

R is selected from the group consisting of isopropyl, cyclobutyl, cyclopentyl, and tetrahydro-2H-pyranyl;

R_1 is hydrogen;

R_2 is ER_5;

R_3 is methyl or ethyl;

E is $-CH_2-$; and

R_5 is selected from the group consisting of phenyl, pyrimidin-2-yl, pyridin-2-yl, pyrazin-2-yl, and 5-methylpyrazin-2-yl.

4. The compound of claim 1, selected from the group consisting of:

6-[(3S,4S)1-benzyl-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-[(3S,4S)-4-methyl-1-(4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-benzimidazol-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(cinnolin-3-ylmethyl)-4-methylpyrrolidin-3-yl]-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-cyclopentyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; and

1-cyclopentyl-6-[(3S,4S)-1-{[2-(dimethylamino)pyrimidin-4-yl]methyl}-4-methylpyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, selected from the group consisting of:

6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-isopropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinoxalin-6-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,5-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[(3S,4S)-4-methyl-1-(1,8-naphthyridin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

1-isopropyl-6-[3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one; and

1-isopropyl-6-[(3S,4S)-4-methyl-1-(pyrido[2,3-b]pyrazin-8-ylmethyl)pyrrolidin-3-yl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, selected from the group consisting of:

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinolin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-4-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-4-methylpyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2,1,3-benzothiadiazol-5-ylmethyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinoxalin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(quinolin-4-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(3-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(35-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[4-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-[(3S,4S)-4-methyl-1-(pyridin-3-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

3-methyl-6-{(3S,4S)-4-methyl-1-[(2-methylpyrimidin-5-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-1-[(6-methoxypyridin-3-yl)methyl]-4-methylpyrrolidin-3-yl}-3-methyl-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[(6-methylpyridin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(4-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-ethylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2-fluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[2-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2,4-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(4-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-benzyl-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-thiopyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(2-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(3-methoxybenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-methyl-1-[3-(trifluoromethyl)benzyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-1-(26-difluorobenzyl)-4-methylpyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-ethyl-1-[(5-methylpyrazin-2-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-{(3S,4S)-4-ethyl-1-[(6-methoxypyridin-3-yl)methyl]pyrrolidin-3-yl}-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-ethyl-1-(pyridin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-ethyl-1-(quinoxalin-2-ylcarbonyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;

2-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile;

3-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile; and

4-({(3S,4S)-3-ethyl-4-[4-oxo-1-(tetrahydro-2H-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl]pyrrolidin-1-yl}methyl)benzonitrile;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable vehicle, carrier or diluent.

8. The composition of claim 7, further comprising a second pharmaceutical agent.

9. The composition of claim 8, wherein the second pharmaceutical agent is selected from the group consisting of donepezil, galantamine, memantine, rivastigmine, and tacrine.

10. A method of inhibiting PDE9 in a mammal in need of such inhibition comprising the step of administering to the mammal PDE9-inhibiting amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof.

11. A method of treating a neurodegenerative disease in a mammal in need of such treatment, comprising the step of administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof.

12. The method of claim 11, wherein the disease is Alzheimer's disease.

13. A method of promoting neurorestoration in a mammal in need of such neurorestoration, comprising the step of administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof.

14. A method of improving cognitive deficits in a mammal in need of such improvement, comprising the step of administering to the mammal a

therapeutically effective amount of a compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof.

15. The method of any one of claims 10-14 wherein the mammal is human.

COMPUESTOS AMINO-HETEROCÍCLICOS

SOLICITUD RELACIONADA

Esta solicitud reivindica el beneficio en virtud de la sección 119(e) del título 35 de USC de la solicitud provisional de EE.UU. nº de serie 60/917.333 presentada el 11 de junio de 2007.

CAMPO DE LA INVENCIÓN

Esta invención se refiere a una serie de compuestos novedosos que son inhibidores selectivos de fosfodiesterasa tipo 9 ("PDE9"). Más particularmente, la invención se refiere a compuestos de pirazolo[3,4-d]pirimidinona para uso en el tratamiento y la prevención de enfermedades neurodegenerativas y otras enfermedades y trastornos influenciados por la modulación de PDE9.

ANTECEDENTES DE LA INVENCIÓN

Los nucleótidos cíclicos guanosina monofosfato cíclico (GMPc) y adenosina monofosfato cíclico (AMPc) son importantes segundos mensajeros y, por tanto, son fundamentales para el control y la regulación de una multitud de eventos celulares, tanto fisiológicos como patofisiológicos, en una amplia variedad de órganos.

El GMP cíclico se forma a partir de GTP mediante la reacción catalítica de la guanilil ciclasa (GC), que se activa por óxido nítrico (NO). El GMP cíclico activa a su vez proteínas quinasas dependientes de GMPc (GKc), que median la señalización localizada y global. Una variedad de procesos fisiológicos en los sistemas cardiovascular, nervioso e inmunitario están controlados por la ruta NO/GMPc, que incluye conductancia de canales de iones, glucogenolisis, apóptosis celular y relajación de músculo liso. En los vasos sanguíneos, la relajación de músculos lisos vasculares lleva a la vasodilatación y al aumento

del flujo sanguíneo.

La familia de enzimas de la fosfodiesterasa (PDE) hidroliza GMPc y AMPc. La enzima PDE9 se ha identificado como un miembro novedoso de la familia de enzimas PDE que hidroliza selectivamente GMPc respecto a AMPc. Véase Fisher *y col., J. Biol. Chem.*, 273(25), 15559-15564 (1998). Se ha encontrado que PDE9 está presente en una variedad de tejidos humanos, concretamente los testículos, cerebro, intestino delgado, músculo esquelético, corazón, pulmón, timo y bazo, además de en células de músculo liso dentro de la vasculatura humana de una variedad de tejidos.

Estudios recientes han implicado directamente la disfunción de la señalización de NO/GMPc/GKc en la enfermedad de Alzheimer. Por ejemplo, se demostró que la alteración de la potenciación a largo plazo (LTP), un correlato fisiológico del aprendizaje y la memoria, mediante el péptido β-amiloide era resultado de una insuficiencia de la señalización de NO/GMPc. Puzzo *y col., J. Neurosci.*, 25(29):6887-6897 (2005). Además, en ratas que mostraban deficiencias en tareas de memoria debido a la disminución de acetilcolinesterasa en el prosencéfalo (que está asociado con enfermedad de Alzheimer), la administración de un mimético de óxido nítrico aumentó la actividad de GC e invirtió las deficiencias cognitivas en tareas de memoria. Bennett *y col., Neuropsychopharmacology*, 32:505-513 (2007). Por tanto, se cree que los agentes terapéuticos que pueden potenciar la cascada de señalización de GC/NO/GMPc/GKc pueden ser útiles como una nueva solución al tratamiento de la enfermedad de Alzheimer y otros trastornos neurodegenerativos.

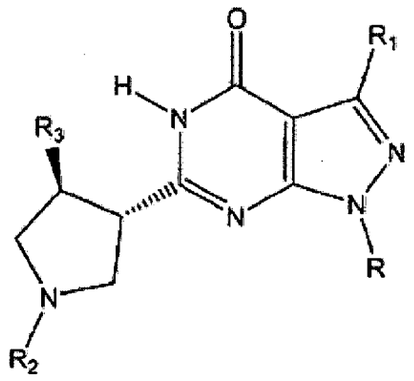
Reduciendo o evitando la hidrólisis de GMPc mediante PDE9, los

inhibidores de PDE9 elevan el nivel intracelular de GMPc, potenciando o prolongando así sus efectos. Se ha encontrado que un aumento en la concentración de GMPc en ratas lleva a una mejora en el aprendizaje y la memoria en pruebas de reconocimiento social y de objetos. Véase, por ejemplo, Boess *y col., Neuropharmacology*, 47:1081-1092 (2004). Se ha demostrado que la inhibición de PDE9 aumenta la LTP. Hendrix, *BMC Pharmacol.*, 5 (sup. 1):55 (2005).

Por consiguiente, existe la necesidad de inhibidores de PDE9 que sean eficaces en el tratamiento de afecciones que pueden regularse o normalizarse mediante la inhibición de PDE9.

RESUMEN DE LA INVENCIÓN

La presente invención se refiere a compuestos de fórmula (I),



(I)

y sales farmacéuticamente aceptables de los mismos, en la que R, R_1, R_2 y R_3 son como se definen en este documento.

La presente invención también se refiere a composiciones que contienen un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un vehículo, excipiente o diluyente farmacéuticamente aceptable, y que además comprenden opcionalmente un segundo agente farmacéutico.

La presente invención se refiere adicionalmente a un procedimiento para inhibir PDE9 en un mamífero en necesidad de tal inhibición, que comprende la etapa de administrar al mamífero una cantidad inhibidora de PDE9 de a) un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo; o b) una composición farmacéutica que comprende un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, y un vehículo, excipiente o diluyente farmacéuticamente aceptable.

La presente invención se refiere adicionalmente a un procedimiento para tratar una enfermedad neurodegenerativa en un mamífero en necesidad de tal tratamiento, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo.

La presente invención se refiere adicionalmente a un procedimiento para promover la neurorrestauración en un mamífero en necesidad de tal neurorrestauración, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo.

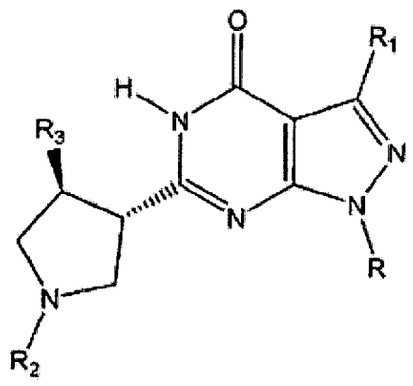
La presente invención todavía se refiere adicionalmente a un procedimiento para mejorar deficiencias cognitivas y tratar alteraciones cognitivas en un mamífero en necesidad de tal mejora o tratamiento, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo.

Con las anteriores y resto de las ventajas y rasgos de la invención que serán evidentes en lo sucesivo, la naturaleza de la invención puede entenderse

más claramente mediante referencia a la siguiente descripción detallada de la invención y las reivindicaciones adjuntas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención comprende novedosos inhibidores de PDE9 selectivos de fórmula (I),



(I)

y sales farmacéuticamente aceptables de los mismos, en los que:

R se selecciona del grupo que está constituido por alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo (C_3-C_8), heterocicloalquilo, arilo y heteroarilo, cada uno de los cuales puede estar opcionalmente sustituido con de uno a tres sustituyentes, seleccionándose independientemente los sustituyentes del grupo que está constituido por alquilo (C_1-C_4), alcoxi (C_1-C_4), halo y haloalquilo (C_1-C_4);

R_1 se selecciona del grupo que está constituido por hidrógeno, alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), haloalquilo (C_1-C_4) y ciclopropilo;

R_2 se selecciona del grupo que está constituido por alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), haloalquilo (C_1-C_6), heteroarilo seleccionado del grupo que está constituido por piridinilo, piridazinilo, pirimidinilo y pirazinilo, y ER_5, en el que el heteroarilo puede estar opcionalmente sustituido con de uno

a tres sustituyentes independientemente seleccionados del grupo que está constituido por alquilo (C_1-C_4) y haloalquilo (C_1-C_4);

R_3 se selecciona del grupo que está constituido por hidrógeno, alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), cicloalquilo (C_3-C_6) y haloalquilo (C_1-C_4);

E se selecciona del grupo que está constituido por -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$- y -C(O)-;

R_5 se selecciona del grupo que está constituido por cicloalquilo (C_3-C_8), heterocicloalquilo, arilo, ariloxi y heteroarilo, cualquiera de los cuales puede estar opcionalmente sustituido con de uno a tres sustituyentes, seleccionándose independientemente tales sustituyentes del grupo que está constituido por alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), hidroxialquilo (C_1-C_4), haloalquilo (C_1-C_4), alcoxi (C_1-C_4), haloalcoxi (C_1-C_4), cicloalquilo (C_3-C_8), halo, ciano, fenilo, morfolinilo, alquil (C_1-C_4)-amino, pirazolilo, triazolilo e imidazolilo.

Preferentemente, R se selecciona del grupo que está constituido por etilo, isopropilo, trifluoroetilo, ciclobutilo, ciclopentilo, difluorociclohexilo, metoxifenilo y tetrahidro-2H-piran-4-ilo; R_1 es hidrógeno o metilo; R_2 es metilo, trifluoroetilo, trifluorobutilo, pirimidinilo, trifluorometilpirimidinilo o ER_5; R_3 es metilo, etilo, isopropilo, trifluorometilo, trifluoroetilo o ciclopropilo; E es -CH_2- o -C(O)-; y R_5 se selecciona del grupo que está constituido por ciclopentilo sustituido o sin sustituir, morfolinilo, fenilo, naftilo, benciloxi, pirimidinilo, piridinilo, quinolinilo, quinoxalinilo, pirazinilo, pirazolilo, bencimidazolilo, cinolinilo, naftidrinilo, pirido[2,3-b]pirazinilo, imidazo[4,5-c]piridinilo, benzotiadiazolilo, tetrahidropirazolo[1,5-a]piridinilo, dihidrobenzodioxinilo,

imidazolilo, dihidrobenzofuranilo, triazolilo, oxazolilo, isoxazolilo, benzodioxinilo, tiazolilo, imidazo[1,2-a]piridinilo, tetrahidrobenzotiazolilo, dihidrobenzoxazinilo, tetrahidropiranilo, tetrahidropirazolo[1,5-a]azepinilo y dihidropirrolo[1,2-b]pirazolilo.

Más preferentemente, R se selecciona del grupo que está constituido por isopropilo, ciclobutilo, ciclopentilo y tetrahidro-2H-piranilo; R_1 es hidrógeno; R_2 es ER_5; R_3 es metilo o etilo; E es $-CH_2-$; y R_5 se selecciona del grupo que está constituido por fenilo, pirimidin-2-ilo, piridin-2-ilo, pirazin-2-ilo y 5-metilpirazin-2-ilo.

En otras realizaciones preferidas, el compuesto es:

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-pirimidin-2-ilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(trifluorometil)pirimidin-2-il]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-benzoil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[3-(trifluorometil)bencil]pirrolidin-3-il}-

1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-{[6-(trifluorometil)piridin-3-il]metil}pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinoxalin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(pirimidin-5-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1,4-dimetilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2,2,2-trifluoroetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpiridin-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-8-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(6-metilpiridin-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-isopropilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-3-metil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-feniletil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(3-metilpiridin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-ciclopropilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3,4-trans)-4-metil-1-(quinolin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3,4-trans)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-

dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3,4-trans)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-(trifluorometil)pirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-(1-bencilpirrolidin-3-il)-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-4-etil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3,4-trans)-4-etil-1-[(6-metoxipiridin-3-il)metil]pirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-4-etil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3S,4S)-4-metil-1-(4,5,6,7-tetrahidropirazolo[1,5-a]piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(1-metil-1H-bencimidazol-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(cinolin-3-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(quinoxalin-6-ilmetil)-4-(trifluorometil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3S,4S)-1-{[2-(dimetilamino)pirimidin-4-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-ciclopropil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-ciclopropil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-ciclopropil-1-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-etil-1,5-dihidro-4H-

pirazolo[3,4-d]pirimidin-4-ona;

6-{(3,4-trans)-4-etil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-(2,2,2-trifluoroetil)pirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(4,4-difluorociclohexil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2,2,2-trifluoroetil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(1,5-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(1,8-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(pirido[2,3-b]pirazin-8-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3,4-trans)-1-[(6-metoxi-1,5-naftiridin-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3,4-trans)-1-[(8-fluoroquinolin-2-il)metil]-4-metilpirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(v)-1-[(6-metoxiquinolin-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclobutil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3,4-trans)-4-etil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(6-metilpiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-{[6-(trifluorometil)piridin-3-il]metil}pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(1-metil-1H-imidazo[4,5-c]piridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclobutil-6-{(3,4-trans)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-

il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2,1,3-benzotiadiazol-5-ilmetil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinoxalin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(3-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(35-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[4-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

3-metil-6-[(3S,4S)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

3-metil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(6-metilpiridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(4-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[2-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2,4-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(4-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-tiopiran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(3-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[3-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2,6-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-etil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-

2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-etil-1-[(6-metoxipiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-etil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-etil-1-(quinoxalin-2-ilcarbonil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

2-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-45-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo;

3-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-45-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo;

4-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-45-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[3-(1H-pirazol-1-il)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpiridin-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(2-cloro-6-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[2-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

1-ciclopentil-6-{(3,4-trans)-1-[(2-etoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,5,6,7-tetrahidropirazolo[1,5-a]piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[4-(1H-imidazol-1-il)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,5-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-metoxi-3-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1-benzofuran-7-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(5-fluoro-2-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-4-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metil-1,3-tiazol-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(4-isopropil-1,3-tiazol-2-il)metil]-4-

metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-difluoro-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-{[6-(1H-pirazol-1-il)piridin-2-il]metil}pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-naftilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(2-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans}-4-metil-1-[4-(1H-1,2,4-triazol-1-il)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-metoxi-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(1-naftilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-4-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,5-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(5-metilisoxazol-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-6-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]-pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,4-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-fluoro-3-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1,4-benzodioxin-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(2-cloro-4-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,4-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,5-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(4-cloro-2-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

3-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo;

1-ciclopentil-6-[(3,4-trans)-1-(2,5-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

2-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-

d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo;

6-[(3,4-trans)-1-(3-cloro-4-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[4-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(3-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,4-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,5-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(3-cloro-2-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(1,3-tiazol-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-2-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(2-etilpirimidin-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-isopropilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(1-etil-1H-pirazol-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(4-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(isoxazol-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-{[6-(1-hidroxi-1-metiletil)piridin-3-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]-4-pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(2,2-dimetil-2,3-dihidro-1-benzofuran-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,4-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(imidazo[1,2-a]piridin-2-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-fenil-1,3-oxazol-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-isopropoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(cinolin-3-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-

dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[3-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-fluoro-3-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(1H-pirazol-1-il)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(2,7-dimetilimidazo[1,2-a]piridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,5-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(4-isopropoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-{[2-(1-hidroxi-1-metiletil)piridin-4-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(mesitilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,6-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

4-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo;

1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-5-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,6-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(4-metoxi-3,5-dimetilpiridin-2-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3-4-trans)-1-(3,5-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,4-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(1-metil-1H-bencimidazol-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(4-metil-3,4-dihidro-2H-1,4-benzoxazin-7-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(3-fenilpropil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[2-(trifluorometil)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,4,4-trifluorobutil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(ciclopentilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,4-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(morfolin-4-ilmetil)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(2,1,3-benzotiadiazol-5-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3,4-trans)-1-[2-(benciloxi)etil]-4-metilpirrolidin-3-il}-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,6-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(3,5,6-trimetilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,4-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(5,6,7,8-tetrahidro-4H-pirazolo[1,5-a]azepin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3-fluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1-benzofuran-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-metoxi-5-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(2-fluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(2-clorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-

dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,4-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3,4-trans)-1-(2,1,3-benzotiadiazol-4-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-propilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-1-[(1-etil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[2-(trifluorometoxi)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(trifluorometil)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(1-metil-1H-imidazo[4,5-c]piridin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3,4-trans)-1-(3,5-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona; o

1-ciclopentil-6-[(3,4-trans)-1-(5,6-dihidro-4H-pirrolo[1,2-b]pirazol-3-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

o una sal farmacéuticamente aceptable de los mismos.

Se ha encontrado sorprendentemente que los compuestos de la invención muestran actividad farmacológica, que incluye inhibir selectivamente PDE9, lo que los hace adecuados para el tratamiento, prevención y/o control en el tratamiento de afecciones que pueden regularse o normalizarse mediante la inhibición de PDE9.

Los compuestos y productos intermedios de la presente invención pueden nombrarse tanto según los sistemas de nomenclatura IUPAC (Unión Internacional de Química Pura y Aplicada) como CAS (Servicio de Resúmenes Químicos, Columbus, OH).

Definiciones

Ciertos términos usados en este documento se definen generalmente del siguiente modo:

El contenido de átomos de carbono de los diversos restos que contienen hidrocarburos en este documento puede indicarse mediante un sufijo que designa en número mínimo y máximo de átomos de carbono en el resto. Por tanto, por ejemplo, alquilo (C_1-C_6) se refiere a un grupo alquilo de uno a seis átomos de carbono, ambos inclusive.

El término "alcoxi" se refiere a un radical de hidrocarburo alifático saturado monovalente lineal o ramificado unido a un átomo de oxígeno que está unido a una estructura central. Ejemplos de grupos alcoxi incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi, isobutoxi, *terc*-butoxi, pentoxi y similares.

El término "alquilo" significa un radical de hidrocarburo alifático saturado monovalente lineal o ramificado. Ejemplos de grupos alquilo incluyen metilo, etilo, propilo, isopropilo, butilo, isobutilo, *terc*-butilo, *sec*-butilo, pentilo, isopentilo, neopentilo, hexilo, isohexilo y similares.

El término "alquenilo" significa un radical de hidrocarburo alifático parcialmente insaturado lineal o ramificado que tiene uno o más dobles enlaces. Ejemplos de grupos alquenilo incluyen etenilo (también conocido como "vinilo"), alilo, 1-propenilo, isopropenilo, *n*-butenilo, *n*-pentenilo y similares. El término "alquenilo" engloba radicales que tienen orientaciones "*cis*"

y "*trans*", o alternativamente orientaciones "*Z*" y "*E*".

El término "alquinilo" significa un radical de hidrocarburo alifático parcialmente insaturado lineal o ramificado que tiene uno o más dobles enlaces. Ejemplos de grupos alquinilo incluyen 1-propinilo, 2-propinilo (también conocido como "propargilo"), 1-butinilo, 2-butinilo, 1-pentinilo y similares.

El término "arilo" denota un sistema de anillo aromático monocíclico o policíclico, por ejemplo, antracenilo, bencilo, fluorenilo, indenilo, naftilo, fenantrenilo, fenilo y similares. El término "arilo" también pretende incluir los derivados parcialmente hidrogenados de tales sistemas de anillo, por ejemplo 1,2,3,4-tetrahidronaftilo.

El término "ariloxi" denota un radical arilo unido a un átomo de oxígeno que está unido a una estructura central, tal como benciloxi.

El término "cicloalquilo" denota un grupo cicloalquilo saturado monocíclico o bicíclico. Ejemplos de grupos cicloalquilo incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y similares.

El término "halógeno" o "halo" representa átomos y radicales de cloro, bromo, flúor y yodo.

El término "haloalquilo" se refiere a un sustituyente alquilo o cicloalquilo en el que al menos un radical hidrógeno está reemplazado con un radical halógeno. Si más de un hidrógeno está reemplazado con halógeno, los halógenos pueden ser iguales o diferentes. Ejemplos de radicales haloalquilo incluyen trifluorometilo, 2,2,2-trifluoroetilo, 4,4,4-trifluorobutilo, 4,4-difluorociclohexilo, clorometilo, diclorometilo, triclorometilo, 1-bromoetilo y similares.

El término "haloalcoxi" se refiere a un radical alcoxi en que al menos un

radical hidrógeno está reemplazado con un radical halógeno. Si más de un hidrógeno está reemplazado con halógeno, los halógenos pueden ser iguales o diferentes. Ejemplos de radicales haloalcoxi incluyen difluorometoxi, trifluorometoxi, 2,2,2-trifluoroetoxi, clorometoxi, bromometoxi y similares.

El término "heteroarilo" como se usa en este documento incluye sistemas de anillo insaturado heterocíclico que contienen uno o más heteroátomos tales como nitrógeno, oxígeno y azufre. Si el grupo heteroarilo contiene más de un heteroátomo, los heteroátomos pueden ser iguales o diferentes. Los radicales heteroarilo pueden estar unidos mediante un átomo de carbono o un heteroátomo. El término "heteroarilo" también pretende incluir los derivados parcialmente hidrogenados de tales sistemas de anillo. Ejemplos de grupos heteroarilo incluyen furanilo (también conocido como "furilo"), imidazolinilo, imidazolilo (también conocido como "1,3-diazolilo"), indolilo, oxadiazolilo, oxazinilo, oxazolilo, isoxazolilo, piranilo, pirazinilo (también conocido como "1,4-diazinilo"), pirazolilo (también conocido como "1,2-diazolilo"), pirazolinilo, pirazilo, piridazinilo (también conocido como "1,2-diazinilo"), piridilo (también conocido como piridinilo), pirimidinilo (también conocido como "1,3-diazinilo" y "pirimidilo"), pirrolilo, tiadiazinilo, tiadiazolilo, tiatriazolilo, tiazolilo, isotiazolilo, tienilo, tiofuranilo (también conocido como "tiofenilo"), tiopiranilo, triazinilo, triazolilo y similares.

El término "heteroarilo" también engloba radicales en los que 2 ó 3 anillos están condensados juntos, en los que al menos tal anillo contiene un heteroátomo como un átomo de anillo, que incluye radicales en los que (a) un anillo heterocicloalquilo está condensado con un anillo arilo o heteroarilo, o (b) un anillo cicloalquilo está condensado con un anillo heteroarilo. Ejemplos de

heteroarilos de 2 anillos condensados incluyen benzodioxinilo, dihidrobenzodioxinilo, benzofuranilo, dihidrobenzofuranilo, isobenzofuranilo, bencimidazolilo, benzotiadiazolilo, tetrahidrobenzotiadiazolilo, benzotiazolilo, benzotienilo (también conocido como "benzotiofenilo," "tionaftenilo" y "benzotiofuranilo"), benzoxazinilo, dihidrobenzoxazinilo, benzoxazolilo, cromanilo, isocromanilo, cromenilo, cinolinilo (también conocido como "1,2-benzodiazinilo"), imidazopiridinilo (por ejemplo imidazo[1,2-a]piridinilo o imidazo[4,5-c]piridinilo), indazolilo, indolinilo, isoindolinilo, indolizinilo, indolilo, isoindolilo, naftiridinilo, oxatiolopirrolilo, pteridinilo, ftalazinilo, purinilo (también conocido como "imidazo[4,5-d]pirimidinilo"), piranopirrolilo, pirazoloazepinilo, tetrahidropirazoloazepinilo (por ejemplo tetrahidropirazolo[1,5-a]azepinilo), pirazolopiridinilo, tetrahidropirazolopiridinilo (por ejemplo tetrahidropirazolo[1,5-a]piridinilo), pirazolopirimidinilo (por ejemplo pirazolo[3,4-d]pirimidinilo), piridopirazinilo (por ejemplo pirido[2,3-b]pirazinilo), piridopiridinilo, pirrolopirazolilo, dihidropirrolopirazolilo (por ejemplo dihidropirrolo[1,2-b]pirazolilo), quinazolinilo (también conocido como "1,3-benzodiazinilo"), quinolinilo (también conocido como "1-benzazinilo"), isoquinolinilo (también conocido como "2-benzazinilo"), quinolizinilo, quinolilo, isoquinolilo, quinoxalinilo, ditianaftalenilo, tienofuranilo (por ejemplo tieno[3,2-b]furanilo) y similares.

Ejemplos de heteroarilos de 3 anillos condensados incluyen acridinilo, diazaantrilo, triazafenantreno, carbazolilo, carbolinilo, furocinolinilo, perimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, tiantrenilo, xantrenilo y similares.

El término "heterocicloalquilo" denota un grupo cicloalquilo saturado

monocíclico o policíclico, en el que al menos uno de los átomos de carbono está reemplazado con un heteroátomo tal como nitrógeno, oxígeno o azufre. Si el heterociclo contiene más de un heteroátomo, los heteroátomos pueden ser iguales o diferentes. Los radicales heterocicloalquilo pueden estar unidos mediante un átomo de carbono o un heteroátomo. Ejemplos de grupos heterocicloalquilo incluyen azetidinilo, dioxaciclohexilo, 1,3-dioxolanilo, imidazolidinilo, morfolinilo, piperazinilo, piperidinilo, pirazolidinilo, pirrolidinilo, tetrahidrofuranoílo, tetrahidropiranilo, tetrahidrotiopiranilo, tiazanilo y similares.

Un grupo cíclico puede estar unido a otro grupo en más de un modo. Si no se especifica una disposición de unión particular, entonces se piensa en todas las disposiciones posibles. Por ejemplo, el término "piridilo" incluye 2-, 3- o 4-piridilo (2-, 3- o 4-piridinilo).

El término "mamífero" significa animales que incluyen, por ejemplo, perros, gatos, vacas, ovejas, cabras, caballos y seres humanos. Los mamíferos preferidos incluyen seres humanos.

El término "oxo" significa un grupo carbonilo formado por la combinación de un átomo de carbono y un átomo de oxígeno.

El término "paciente" incluye pacientes tanto humanos como no humanos.

La frase "farmacéuticamente aceptable" indica que el excipiente, vehículo, diluyente y/o sal designados es generalmente química y/o físicamente compatible con el resto de componentes que comprenden la formulación, y es fisiológicamente compatible con el receptor de la misma.

El término "sales" se refiere a sales tanto orgánicas como inorgánicas de un compuesto de fórmula (I). Tales sales pueden prepararse *in situ* durante el

aislamiento y purificación final de un compuesto, o haciendo reaccionar por separado un compuesto, profármaco o estereoisómero de fórmula (I) con un ácido o base orgánico o inorgánico adecuado y aislando la sal así formada. Sales aniónicas representativas incluyen las sales de bromhidrato, clorhidrato, yodhidrato, sulfato, bisulfato, nitrato, acetato, trifluoroacetato, oxalato, besilato, palmitato, pamoato, malonato, estearato, laurato, malato, borato, benzoato, lactato, fosfato, hexafluorofosfato, bencenosulfonato, tosilato, formiato, citrato, maleato, fumarato, succinato, tartrato, naftilato, mesilato, glucoheptonato, lactobionato y lauril sulfonato y similares. Sales catiónicas representativas incluyen las sales de sodio, potasio, calcio y magnesio y similares. Véase generalmente, por ejemplo, Berge *y col.*, *J. Pharm. Sci*, 66, 1-19 (1977).

Una sal de un compuesto de fórmula (I) puede prepararse fácilmente mezclando disoluciones de un compuesto de fórmula (I) y el ácido o base deseado, según convenga. La sal puede precipitar en la disolución y recogerse mediante filtración o puede recuperarse mediante evaporación del disolvente.

El término "radical" denota un grupo de átomos que se comporta como un único reactivo en una reacción química, por ejemplo, un radical orgánico es un grupo de átomos que confiere propiedades características a un compuesto que lo contiene, o que permanece sin variaciones durante una serie de reacciones o transformaciones.

El símbolo "-" representa un enlace covalente.

La frase "disolvente inerte a la reacción" o "disolvente inerte" se refiere a un disolvente, o mezcla de disolventes, que no interacciona con los materiales de partida, reactivos, productos intermedios o productos de un modo que afecte adversamente sus propiedades deseadas.

Los términos "tratar," "tratando," "tratado" o "tratamiento" como se usan en este documento incluyen usos o resultados preventivos (por ejemplo, profilácticos), paliativos o curativos.

Los compuestos de fórmula (I) pueden contener centros asimétricos o quirales y, por tanto, existen en diferentes formas estereoisoméricas. Aquellos expertos en la materia apreciarán que, a menos que se especifique lo contrario, todos los estereoisómeros (por ejemplo, enantiómeros y diastereoisómeros, y mezcla racémicas de los mismos) de los compuestos novedosos y productos intermedios descritos, ilustrados y/o tratados en este documento están dentro del alcance de la invención reivindicada. Además, a menos que se especifique lo contrario, la presente invención engloba todos los isómeros geométricos y de posición. Se prefiere el enantiómero (3S,4S) de la configuración de pirrolidinilo central.

Las mezclas diastereoméricas pueden separarse en sus diastereómeros individuales basándose en sus diferencias fisico-químicas mediante procedimientos muy conocidos para aquellos expertos en la materia, tales como mediante cromatografía y/o cristalización fraccionada. Los enantiómeros pueden separarse convirtiendo la mezcla enantiomérica en una mezcla diastereomérica mediante reacción con un compuesto ópticamente activo apropiado (por ejemplo, alcohol), separando los diastereómeros y convirtiendo (por ejemplo, hidrolizando) los diastereómeros individuales en los enantiómeros puros correspondientes. Procedimientos adicionales incluyen la resolución de mezclas racémicas usando sales quirales, además de cromatografía quiral.

Aquellos expertos en la materia reconocerán adicionalmente que los compuestos de fórmula (I) pueden existir en forma cristalina como hidratos, en

los que las moléculas de agua están incorporadas dentro de la estructura cristalina de los mismos, y como solvatos, en los que las moléculas de un disolvente están incorporadas en su interior. Todas las formas de hidrato y solvato se consideran parte de esta invención.

Los médicos apreciarán que ciertos compuestos de fórmula (I) pueden existir como isómeros tautoméricos, es decir, que el equilibrio existe entre dos isómeros que están en rápido equilibrio entre sí. Un ejemplo común de tautomería es la tautomería ceto-enólica, es decir,



El grado en el que un tautómero está presente respecto al otro depende de diversos factores, que incluyen el modelo de sustitución y tipo de disolvente. Otros ejemplos según la presente invención serán reconocidos por aquellos expertos en la materia. Todas las formas tautómeras de fórmula (I) están incluidas dentro del alcance de la invención, a menos que se especifique lo contrario.

La presente invención también incluye profármacos de los compuestos de la invención. El término "profármaco" se refiere a un precursor de fármaco que, tras la administración, libera el fármaco *in vivo* mediante un proceso químico o fisiológico (por ejemplo, llevándose a pH fisiológico o mediante actividad enzimática). El profármaco puede ser por sí mismo biológicamente activo, o puede convertirse en un compuesto biológicamente activo (por ejemplo mediante metabolismo o hidrólisis) durante su tiempo de permanencia en el cuerpo. Una discusión de la preparación y uso de profármacos se

proporciona por Higuchi y Stella, "Prodrugs as Novel Delivery Systems", vol. 14 de A.C.S. Symposium Series, y en "Bioreversible Carriers in Drug Design," ed. Edward B. Roche, American Pharmaceutical Association y Pergamon Press, 1987. Todos los profármacos de los diversos compuestos de fórmula (I) están dentro del alcance de la presente invención.

La presente invención también engloba compuestos de fórmula (I) isotópicamente marcados que son idénticos a aquellos referidos en este documento, salvo por el hecho de que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o número másico normalmente encontrado en la naturaleza. Ejemplos de isótopos que pueden incorporarse en los compuestos de fórmula (I) incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}o, ^{17}o, ^{31}P, ^{32}P, ^{35}S, ^{18}F y ^{36}Cl, respectivamente. Los compuestos de fórmula (I), y sales farmacéuticamente aceptables de los mismos, que contienen los isótopos anteriormente mencionados y/u otros isótopos de otros átomos están dentro del alcance de la presente invención.

Ciertos compuestos isotópicamente marcados de fórmula (I), por ejemplo aquellos en los que se incorporan isótopos radiactivos tales como ^{3}H y ^{14}C, son útiles en ensayos de distribución en tejidos de fármacos y/o sustratos. Se prefieren particularmente isótopos tritiados, es decir, ^{3}H y ^{14}C, debido a su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio, es decir, ^{2}H, puede dar ciertas ventajas terapéuticas resultantes de mayor estabilidad metabólica, por ejemplo, aumento de la semivida *in vivo*, o reducción de los requisitos de dosificación y,

por tanto, pueden preferirse en algunas circunstancias. Los compuestos isotópicamente marcados de fórmula (I), y sales farmacéuticamente aceptables de los mismos, pueden prepararse generalmente llevando a cabo procedimientos análogos a aquellos descritos en los esquemas y/o en los ejemplos de más adelante, mediante sustitución de un reactivo no isotópicamente marcado por un reactivo isotópicamente marcado fácilmente disponible.

La invención también incluye composiciones farmacéuticas que comprenden una cantidad de un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del compuesto, y opcionalmente un vehículo, excipiente o diluyente farmacéuticamente aceptable. En una realización preferida, la composición farmacéutica es de una cantidad eficaz para la inhibición de la enzima PDE9 en un mamífero. En otra realización preferida, el mamífero es un ser humano.

La presente invención incluye el uso de una combinación de un compuesto inhibidor de PDE9 como se proporciona en la fórmula (I) y uno o más agentes farmacéuticamente activos adicionales. Si se administra una combinación de agentes activos, entonces pueden administrarse secuencialmente o simultáneamente, en formas farmacéuticas separadas o combinadas en una única forma farmacéutica. Por consiguiente, la presente invención también incluye composiciones farmacéuticas que comprenden una cantidad de: (a) un primer agente que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del compuesto; (b) un segundo agente farmacéuticamente activo; y (c) un excipiente, vehículo o diluyente farmacéuticamente aceptable.

Pueden seleccionarse diversos agentes farmacéuticamente activos para uso conjunto con los compuestos de fórmula (I) dependiendo de la enfermedad, trastorno o afección que vaya a tratarse. Agentes farmacéuticamente activos que pueden usarse en combinación con las composiciones de la presente invención incluyen, sin limitación:

(i) inhibidores de la acetilcolinesterasa, tales como clorhidrato de donepezilo (E2020, ARICEPT, MEMAC), salicilato de fisostigmina (ANTILIRIUM), sulfato de fisostigmina (ESERINE), metrifonato, neostigmina, piridostigmina (MESTINON), ambenonio (MYTELASE), demarcario, Debio992 (también conocido como ZT-1), rivastigmina (EXELON), ladostigil (también conocido como TV3326), NP-0361, bromhidrato de galantamina (RAZADYNE, RIMINYL, NIVALIN), tacrina (COGNEX), maleato de velnacrina, memoquina, huperzina A (HUP-A), fenserina y edrofonio (ENLON, TENSILON);

(ii) β-amiloide (o fragmentos del mismo), tales como $A\beta_{1-15}$ conjugado con epítopo de unión a pan HLA-DR (PADRE), ACC-001, ACI-01, ACI-24, AN-1792, Affitope AD-01, CAD106 y V-950;

(iii) anticuerpos contra β-amiloide (o fragmentos del mismo), tales como bapineuzumab (también conocido como AAB-001), AAB-002, ACI-01-Ab7, BAN-2401, Ig intravenosa (GAMMAGARD), LY2062430 (m266 humanizado), PF-04360365 (también conocido como RN-1219), RN-6G, R-1450, ACU-5ª5, huC091, y aquellos descritos en las publicaciones de patente internacional n$^{ros.}$ WO04/032868, WO05/025616, WO06/036291, WO06/069081, WO06/118959, en las publicaciones de patente de EE.UU. n$^{ros.}$ US2003/0073655, US2004/0192898, US2005/0048049, US2005/0019328, en las publicaciones de patente europea n$^{ros.}$ EP0994728 y 1257584 y en la patente de EE.UU. nº

5.750.349;

(iv) agentes reductores o inhibidores de amiloides (incluyendo aquellos que reducen la acumulación y fibrilación de amiloides) tales como bisnorcimserina (también conocida como BNC), pioglitazona, PBT2, flurbiprofeno (ANSAID, FROBEN) y su enantiómero *R* tarenflurbilo (también conocido como MPC-7869; FLURIZAN), nitroflurbiprofeno, fenoprofeno (FENOPRON, NALFON), ibuprofeno (ADVIL, MOTRIN, NUROFEN), lisinato de ibuprofeno, ácido meclofenámico, meclofenamato sódico (MECLOMEN), indometacina (INDOCIN), diclofenac sódico (VOLTAREN), diclofenac potásico, sulindac (CLINORIL), sulfuro de sulindac, diflunisal (DOLOBID), naproxen (NAPROSYN), naproxen sódico (ANAPROX, ALEVE), enzima degradadora de insulina (también conocida como insulisina), el extracto de gingko biloba EGb-761 (ROKAN, TEBONIN), tramiprosato (NC-758, CEREBRIL, ALZHEMED), eprodisato (NC-503, FIBRILLEX, KIACTA), compuesto W (ácido 3,5-bis(4-nitrofenoxi)benzoico), NGX-96992, neprilisina (también conocida como endopeptidasa neutra (NEP)), escilo-inositol (también conocido como escilitol, ELND005, AZD-103), atorvastatina (LIPITOR), sinvastatina (ZOCOR), KLVFF-(EEX)3 e inhibidores de RAGE (receptor para productos finales de glicación avanzada);

(v) agonistas de los receptores alfa-adrenérgicos, tales como clonidina (CATAPRES), metaraminol (ARAMINE), metildopa (ALDOMET, DOPAMET, NOVOMEDOPA), tizanidina (ZANAFLEX), fenilefrina (también conocida como neosinefrina), metoxamina, cirazolina, guanfacina (INTUNIV), lofexidina, xilazina, modafinilo (PROVIGIL), adrafinilo y armodafinilo (NUVIGIL);

(vi) agentes bloqueantes de los receptores beta-adrenérgicos (beta

bloqueantes) tales como carteolol, esmolol (BREVIBLOC), labetalol (NORMODYNE, TRANDATE), oxprenolol (LARACOR, TRASACOR), pindolol (VISKEN), propanolol (INDERAL), sotalol (BETAPACE, SOTALEX, SOTACOR), timolol (BLOCADREN, TIMOPTIC), acebutolol (SECTRAL, PRENT), nadolol (CORGARD), tartrato de metoprolol (LOPRESSOR), succinato de metoprolol (TOPROL-XL), atenolol (TENORMIN), butoxamina y SR 59230ª (Sanofi);

(vii) anticolinérgicos, tales como amitriptilina (ELAVIL, ENDEP), butriptilina, mesilato de benztropina (COGENTIN), trihexifenidilo (ARTANE), difenhidramina (BENADRYL), orfenadrina (NORFLEX), hiosciamina, atropina (ATROPEN), escopolamina (TRANSDERM-SCOP), metilbromuro de escopolamina (PARMINE), diciclovérina (BENTYL, BYCLOMINE, DIBENT, DILOMINE), tolterodina (DETROL), oxibutinina (DITROPAN, LYRINEL XL, OXITROL), bromuro de pentienato, propantelina (PRO-BANTHINE), ciclizina, clorhidrato de imipramina (TOFRANIL), maleato de imipramina (SURMONTIL), lofepramina, desipramina (NORPRAMIN), doxepina (SINEQUAN, ZONALON), trimipramina (SURMONTIL) y glicopirrolato (ROBINUL);

(viii) anticonvulsivos, tales como carbamazepina (TEGRETOL, CARBATROL), oxcarbazepina (TRILEPTAL), fenitoína sódica (PHENYTEK), fosfenitoína (CEREBYX, PRODILANTIN), divalproex sódico (DEPAKOTE), gabapentina (NEURONTIN), pregabalina (LYRICA), topirimato (TOPAMAX), ácido valproico (DEPAKENE), valproato sódico (DEPACON), 1-bencil-5-bromouracilo, progabida, beclamida y primidona (MYSOLINE);

(ix) antipsicóticos, tales como lurasidona (también conocida como SM-13496), aripiprazol (ABILIFY), clorpromazina (THORAZINE), haloperidol

(HALDOL), decanoato de flupentixol (DEPIXOL, FLUANXOL), reserpina (SERPLAN), pimozida (ORAP), decanoato de flufenazina, clorhidrato de flufenazina, proclorperazina (COMPRO), asenapina, loxapina (LOXITANE), mesoridazina, molindona (MOBAN), perfenazina, tioridazina, tiotixina, trifluoperazina (STELAZINE), clozapina (CLOZARIL), norclozapina (ACP-104), risperidona (RISPERDAL), paliperidona (INVEGA), melperona, olanzapina (ZYPREXA), quetiapina (SEROQUEL), sertindol, sulpirida (MERESA, DOGMATYL, SULPITIL), amisulprida, ziprasidona (GEODON), blonanserina (LONASEN) y bifeprunox;

(x) bloqueantes de los canales de calcio tales como nilvadipina (ESCOR, NIVADIL), amlodipina (NORVASC, ISTIN, AMLODIN), felodipina (PLENDIL), nicardipina (CARDENE), nifedipina (ADALAT, PROCARDIA), MEM 1003 y su compuesto parental nimodipina (NIMOTOP), nisoldipina (SULAR), nitrendipina, lacidipina (LACIPIL, MOTENS), lercanidipina (ZANIDIP), diltiazem (CARDIZEM), verapamilo (CALAN, VERELAN) y enecadina (también conocida como NS-7);

(xi) inhibidores de la catecol-O-metiltransferasa (COMT), tales como tolcapona (TASMAR), entacapona (COMTAN) y tropolona;

(xii) estimulantes del sistema nervioso central, tales como cafeína, fenmetrazina, fendimetrazina, pemolina, fencamfamina (GLUCOENERGAN, REACTIVAN), fenetilina (CAPTAGON), pipradol (MERETRAN), deanol (también conocido como dimetilaminoetanol), metilfenidato (DAYTRANA), clorhidrato de metilfenidato (RITALIN), dexmetilfenidato (FOCALIN), anfetamina (sola o en combinación con otros estimulantes del SNC, por ejemplo ADDERALL (aspartato de anfetamina, sulfato de anfetamina, sacarato de

dextroanfetamina y sulfato de dextroanfetamina)), sulfato de dextroanfetamina (DEXEDRINE, DEXTROSTAT), metanfetamina (DESOXYN), lisdexanfetamina (VYVANSE) y benzfetamina (DIDREX);

(xiii) corticosteroides, tales como prednisona (STERAPRED, DELTASONE), prednisolona (PRELONE), acetato de prednisolona (OMNIPRED, PRED MILD, PRED FORTE), fosfato sódico de prednisolona (ORAPRED ODT), metilprednisolona (MEDROL); acetato de metilprednisolona (DEPO-MEDROL) y succinato sódico de metilprednisolona (A-METHAPRED, SOLU-MEDROL);

(xiv) agonistas de los receptores de dopamina, tales como apomorfina (APOKYN), bromocriptina (PARLODEL), cabergolina (DOSTINEX), dihidrexidina, dihidroergocriptina, fenoldopam (CORLOPAM), lisurida (DOPERGIN), pergolida (PERMAX), piribedil (TRIVASTAL, TRASTAL), pramipexol (MIRAPEX), quinpirol, ropinirol (REQUIP) y rotigotina (NEUPRO);

(xv) antagonistas de los receptores de dopamina, tales como tetrabenazina (NITOMAN, XENAZINE), 7-hidroxiamoxapina, droperidol (INAPSINE, DRIDOL, DROPLETAN), domperidona (MOTILIUM), L-741742, L-745870, racloprida, SCH-23390, ecopipam, SKF-83566 y metoclopramida (REGLAN);

(xvi) inhibidores de la recaptación de dopamina tales como maleato de nomifensina (MERITAL), vanoxerina (también conocida como GBR-12909) y su éster decanoato DBL-583 y amineptina;

(xvii) agonistas del receptor del ácido gamma-aminobutírico (GABA), tales como baclofen (LIORESAL, KEMSTRO), pentobarbital (NEMBUTAL), progabida (GABRENE) y clometiazol;

(xviii) inmunomoduladores tales como acetato de glatiramer (también conocido como copolímero-1; COPAXONE), MBP-8298 (péptido sintético de la proteína básica de la mielina), fumarato de dimetilo, fingolimod (también conocido como FTY720), roquinimex (LINOMIDE), laquinimod (también conocido como ABR-215062 y SAIK-MS), ABT-874 (anticuerpo humano anti-IL-12), rituximab (RITUXAN), alemtuzumab (CAMPATH), daclizumab (ZENAPAX) y natalizumab (TYSABRI);

(xix) inmunodepresores tales como metotrexato (TREXALL, RHEUMATREX), mitoxantrona (NOVANTRONE), micofenolato mofetil (CELLCEPT), micofenolato sódico (MYFORTIC), azatioprina (AZASAN, IMURAN), mercaptopurina (PURI-NETHOL), ciclofosfamida (NEOSAR, CYTOXAN), clorambucilo (LEUKERAN), cladribina (LEUSTATIN, MILINAX), alfa-fetoproteína, etanercept (ENBREL) y 4-benciloxi-5-((5-undecil-2H-pirrol-2-iliden)metil)-2,2'-bi-1H-pirrol (también conocido como PNU-156804);

(xx) interferones, que incluyen interferón beta-1ª (AVONEX, REBIF) e interferón beta-1b (BETASERON, BETAFERON);

(xxi) levodopa (o su éster etílico o metílico), sola o en combinación con un inhibidor de DOPA descarboxilasa (por ejemplo carbidopa (SINEMET, CARBILEV, PARCOPA, V1512), benserazida (MADOPAR), α-metildopa, monoflurometildopa, difluorometildopa, brocresina o m-hidroxibencilhidrazina);

(xxii) antagonistas del receptor de *N*-metil-D-aspartato (NMDA), tales como memantina (NAMENDA, AXURA, EBIXA), amantadina (SYMMETREL), acamprosato (CAMPRAL), besonprodil (también conocido como PD-196.860 o CI-1041), ketamina (KETALAR), delucemina (también conocida como NPS 1506), dexanabinol (también conocido como HU-211), dextrometorfano,

dextrorfano, traxoprodil (también conocido como CP-101.606), himantano, idantadol (también conocido como V-3381), lancicemina (también conocida como AR-R 15896), levorfanol (DROMORAN), metadona, (DOLOPHINE), neramexano (también conocido como MRZ 2/579), perzinfotel, fenciclidina, tianeptina (STABLON), dizocilpina (también conocida como MK-801), ibogaína, voacangina, tiletamina, riluzol (RILUTEK), aptiganel (CERESTAT), gavestinel y remacimida;

(xxiii) inhibidores de la monoamina oxidasa (MAO), tales como selegilina (EMSAM), clorhidrato de selegilina (l-deprenilo, ELDEPRYL, ZELAPAR), dimetilselegileno, brofaromina, fenelzina (NARDIL), tranilcipromina (PARNATE), moclobemida (AURORIX, MANERIX), befloxatona, safinamida (también conocida como PNU-151774E), isocarboxazida (MARPLAN), nialamida (NIAMID), rasagelina (AZILECT), iproniazida (MARSILID, IPROZID, IPRONID), iproclozida, toloxatona (HUMORYL, PERENUM), bifemelano, desoxipeganina, harmina (también conocida como telepatina o banasterina), harmalina, linezolid (ZYVOX, ZYVOXID) y pargilina (EUDATIN, SUPIRDYL);

(xxiv) agonistas de los receptores muscarínicos (particularmente el subtipo M1), tales como cloruro de betanecol (DUVOID, URECHOLINE), pilocarpina (SALAGEN), NGX267, arecolina, L-687306, L-689660, yoduro de furtretonio (FURAMON, FURANOL), bencenosulfonato de furtretonio, *p*-toluenosulfonato de furtretonio, McN-A-343, oxotremorina y carbacol (CARBASTAT, MIOSTAT, CARBOPTIC);

(xxv) agonistas de los receptores nicotínicos, tales como epibatidina, ABT-089, ABT-594, AZD-0328, R-4996 (también conocida como MEM-63908), TC-5619 y EVP-6124;

(xxvi) fármacos neuroprotectores tales como oxima de 2,3,4,9-tetrahidro-1*H*-carbazol-3-ona, AL-108, ACD3480 (también conocido como TC-1734), bis(4-β-D-glucopiranosiloxibencil)-2-β-D-glucopiranosil-2-isobutiltartrato (también conocido como dactilorina B o DHB), xaliprodeno (XAPRILA), clorhidrato de dimebolina (DIMEBON), disufentona (NXY-059, CEROVIVE), ácido arúndico (ONO-2506, PROGLIA, CEREACT), citicolina (también conocida como 5'-difosfocolina de citidina), edaravona (RADICUT), AEOL-10150, AGY-94806 (también conocido como SA-450 y Msc-1), factor estimulante de colonias de granulocitos (AX-200), BAY-387271 (también conocido como KN-387271), DP-b99, HF-0220 (17-β-hidroxiepiandrosterona), HF-0420 (también conocido como oligotropina), 5'-fosfato de piridoxal (también conocido como MC-1), microplasmina, S-18986, piclozotan (también conocido como SUN-N4057), NP031112, L-seril-L-metionil-L-alanil-L-lisil-L-glutamil-glicil-L-valina y SUN-N8075;

(xxvii) inhibidores de la recaptación de norepinefrina (noradrenalina), tales como atomoxetina (STRATTERA), doxepina (APONAL, ADAPIN, SINEQUAN), nortriptilina (AVENTYL, PAMELOR, NORTRILEN), amoxapina (ASENDIN, DEMOLOX, MOXIDIL), reboxetina (EDRONAX, VESTRA), viloxazina (VIVALAN), maprotilina (DEPRILEPT, LUDIOMIL, PSYMION), bupropion (WELLBUTRIN) y radaxafina;

(xxviii) otros inhibidores de PDE9, tales como BAY 73-6691 y aquellos descritos en la publicación de patente de EE.UU. nº US2003/0195205, US2004/0220186, US2006/0111372 y US2006/0106035;

(xxix) otros inhibidores de la fosfodiesterasa (PDE), que incluyen (a) inhibidores de PDE1 (por ejemplo vinpocetina (CAVINTON, CERACTIN,

INTELECTOL) y aquellos descritos en la patente de EE.UU. nº 6.235.742), (b) inhibidores de PDE2 (por ejemplo eritro-9-(2-hidroxi-3-nonil)adenina (EHNA), BAY 60-7550, y aquellos descritos en la patente de EE.UU. nº 6.174.884), (c) inhibidores de PDE4 (por ejemplo rolipram, Ro 20-1724, ibudilast (KETAS), piclamilast (también conocido como RP73401), CDP840, cilomilast (ARIFLO), roflumilast, tofimilast, oglemilast (también conocido como GRC 3886), tetomilast (también conocido como OPC-6535), lirimifast, teofilina (UNIPHYL, THEOLAIR), arofilina (también conocida como LAS-31025), doxofilina, RPR-122818, o mesembrina), y (d) inhibidores de PDE5 (por ejemplo sildenafilo (VIAGRA, REVATIO), tadalafilo (CIALIS), vardenafilo (LEVITRA, VIVANZA), udenafilo, avanafilo, dipiridamol (PERSANTINE), E-4010, E-4021, E-8010, zaprinast, PF-489791, UK-357903, DA-8159, y aquellos descritos en las solicitudes de patente internacional nº WO05/049616, WO06/120552 y WO07/122466);

(xxx) quinolinas, tales como quinina (incluyendo sus sales de clorhidrato, diclorhidrato, sulfato, bisulfato y gluconato), cloroquina, hidroxicloroquina (PLAQUENIL), mefloquina (LARIAM) y amodiaquina (CAMOQUIN, FLAVOQUINE);

(xxxi) inhibidores de la β-secretasa, tales como WY-25105, tartrato de (+)-fenserina (POSIPHEN), LSN-2434074 (también conocido como LY-2434074), PNU-33312, KMI-574, SCH-745966, Ac-rER (N^2-acetil-D-arginil-L-arginina), loxistatina (también conocida como E64d) y CA074Me;

(xxxii) inhibidores de la γ-secretasa, tales como LY-411.575, LY-685.458, ELAN-G, ELAN-Z, 4-cloro-*N*-[2-etil-1(S)-(hidroximetil)butil]bencenosulfonamida,

(xxxiii) antagonistas de los receptores de serotonina (5-hidroxitriptamina)

1ª (5-HT_{1A}), tales como espiperona, *levo*-pindolol, BMY 7378, NAD-299, S(-)-UH-301, NAN 190, WAY 100635, lecozotan (también conocido como SRA-333);

(xxxiv) antagonistas de los receptores de serotonina (5-hidroxitriptamina) 6 (5-HT_6), tales como mianserina (TORVOL, BOLVIDON, NORVAL), metiotepina (también conocida como metitepina), ritanserina, ALX-1161, ALX-1175, MS-245, LY-483518 (también conocido como SGS518), MS-245, Ro 04-6790, RO 43-68544, Ro 63-0563, RO 65-7199, Ro 65-7674, SB-399885, SB-214111, SB-258510, SB-271046, SB-357134, SB-699929, SB-271046, SB-742457 y PRX-07034;

(xxxv) inhibidores de la recaptación de serotonina (5-HT) tales como alaproclato, citalopram (CELEXA, CIPRAMIL), escitalopram (LEXAPRO, CIPRALEX), clomipramina (ANAFRANIL), duloxetina (CYMBALTA), femoxetina (MALEXIL), fenfluramina (PONDIMIN), norfenfluramina, fluoxetina (PROZAC), fluvoxamina (LUVOX), indalpina, milnacipran (IXEL), paroxetina (PAXIL, SEROXAT), sertralina (ZOLOFT, LUSTRAL), trazodona (DESYREL, MOLIPAXIN), venlafaxina (EFFEXOR), zimelidina (NORMUD, ZELMID), bicifadina, desvenlafaxina (PRISTIQ), brasofensina y tesofensina;

(xxxvi) factores tróficos, tales como factor de crecimiento nervioso (NGF), factor de crecimiento del fibroblasto básico (FGFb), neurotrofina-3 (NT-3), factor neurotrófico derivado del cerebro (BDNF) y factor neurotrófico derivado de la glía (GDNF), y agentes que estimulan la producción local de factores tróficos tales como propentofilina, idebenona y AIT-082 (NEOTROFIN);

y similares.

La invención también incluye procedimientos para inhibir PDE9 en un

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mamífero que comprenden administrar al mamífero en necesidad de tal inhibición una cantidad inhibidora de PDE9 de: (a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo; o (b) una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en un vehículo, excipiente o diluyente farmacéuticamente aceptable; bien solo o en combinación con un segundo agente como se describe anteriormente.

La invención también incluye procedimientos para tratar afecciones mediadas por la inhibición de PDE9 en un mamífero que comprenden administrar al mamífero en necesidad de tal tratamiento una cantidad terapéuticamente eficaz de: (a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo; o (b) una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en un vehículo, excipiente o diluyente farmacéuticamente aceptable; bien solo o en combinación con un segundo agente descrito anteriormente.

Las afecciones que pueden tratarse, controlarse o prevenirse mediante los procedimientos de la presente invención incluyen enfermedades y trastornos asociados con neurodegeneración tales como: enfermedad de Alexander, enfermedad de Alper, enfermedad de Alzheimer, esclerosis lateral amiotrófica (ELA; también conocida como enfermedad de Lou Gehrig o enfermedad de las neuronas motoras), ataxia-telangiectasia, enfermedad de Batten (también conocida como enfermedad de Spielmeyer-Vogt-Sjogren-Batten), demencia de Binswanger (encefalopatía arteriosclerótica subcortical), trastornos bipolares, encefalopatía espongiforme bovina (EEB), enfermedad de

Canavan, demencia inducida por quimioterapia, síndrome de Cockayne, degeneración corticobasal, enfermedad de Creutzfeldt-Jakob, depresión, síndrome de Down, degeneración lobar frontotemporal (incluyendo demencia frontotemporal, demencia semántica y afasia no fluente progresiva), enfermedad de Gerstmann-Straüssler-Scheinker, glaucoma, enfermedad (corea) de Huntington, demencia asociada a VIH, hipercinesias, enfermedad de Kennedy, síndrome de Korsakoff (síndrome amnésico-confabulatorio), enfermedad de Krabbe, demencia con cuerpos de Lewy, afasia progresiva logopénica, enfermedad de Machado-Joseph (ataxia espinocerebelosa tipo 3), esclerosis múltiple, atrofia de múltiples sistemas (atrofia olivopontocerebelosa), miastenia grave, enfermedad de Parkinson, enfermedad de Pelizaeus-Merzbacher, enfermedad de Pick, demencia presenil (deterioro cognitivo leve), esclerosis lateral primaria, afasia progresiva primaria, demencia inducida por radiación, enfermedad de Refsum (enfermedad por almacenamiento de ácido fitánico), enfermedad de Sandhoff, enfermedad de Schilder, esquizofrenia, demencia semántica, demencia senil, síndrome de Shy-Drager, ataxias espinocerebelosas, atrofias musculares espinales, enfermedad de Steele-Richardson-Olszewski (parálisis supranuclear progresiva), tabes dorsal, discinesia tardía, amiloidosis vascular y demencia vascular (demencia multi-infarto).

Preferentemente, la enfermedad o trastorno neurodegenerativo es enfermedad de Alzheimer.

Otras afecciones y trastornos asociados con PDE9 que pueden tratarse o controlarse mediante los procedimientos de la presente invención incluyen trastornos del aparato genitourinario tales como disfunción sexual, trastorno por

déficit de atención (ADD), trastorno por déficit de atención con hiperactividad (ADHD), diabetes, trastornos o enfermedades cardiovasculares tales como hipertensión sistémica, hipertensión pulmonar, insuficiencia cardiaca congestiva, enfermedad de las arterias coronarias, aterosclerosis, accidente cerebrovascular, trombosis, afecciones de permeabilidad reducida de los vasos sanguíneos (por ejemplo angioplastia coronaria transluminal pospercutánea), enfermedad vascular periférica, enfermedad renal, angina (incluyendo angina estable, inestable y variante (Prinzmetal)) y cualquier afección en la que la mejora del flujo sanguíneo lleva a una mejora de la función del órgano final.

La presente invención también se refiere a procedimientos para promover la neurorrestauración y la recuperación funcional en pacientes que padecen lesión traumática o no traumática del cerebro, médula espinal o nervios periféricos. Las lesiones cerebrales traumáticas incluyen tanto lesiones cerradas de cabeza (en la que el cráneo no está roto) como lesiones abiertas o penetrantes de cabeza (en las que un objeto perfora el cráneo y abre una brecha en la duramadre), en las que el traumatismo repentino (por ejemplo, accidentes, caídas, agresiones) producen un daño al tejido cerebral mediante rotura, estiramiento, hematoma o inflamación. Las causas de las lesiones cerebrales no traumáticas incluyen aneurisma, accidente cerebrovascular, meningitis, privación de oxígeno debido a anoxia, hipoxia o isquemia, tumor cerebral, infección (por ejemplo encefalitis), intoxicación, abuso de sustancias y similares. La presente invención es útil para el tratamiento de deterioro cognitivo y disfunción cognitiva resultante de lesiones cerebrales, además de enfermedades y trastornos neurodegenerativos.

La presente invención también se refiere a procedimientos para prevenir

las afecciones anteriormente descritas en un mamífero, que incluye al ser humano, que comprende las etapas de administrar al mamífero una cantidad de: (a) un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo; o (b) una composición farmacéutica que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo, en un vehículo, excipiente o diluyente farmacéuticamente aceptable; bien solo o en combinación con un segundo agente como se describe anteriormente, como parte de una pauta posológica de dosificación apropiada diseñada para prevenir dicha afección.

La presente invención también se refiere a procedimientos para mejorar deficiencias cognitivas que incluyen deficiencias en la percepción, concentración, aprendizaje, memoria, comunicación, razonamiento y resolución de problemas.

La pauta posológica de dosificación apropiada, la cantidad de cada dosis administrada y los intervalos entre dosis del compuesto dependerán, entre otros, del compuesto de fórmula (I) de esta invención que vaya a usarse, el tipo de composiciones farmacéuticas que vayan a usarse, las características del sujeto que vaya a tratarse y el tipo y la gravedad de las afecciones que vayan a tratarse. En general, una dosis eficaz para compuestos de fórmula (I), o sales farmacéuticamente aceptables de los mismos, está en el intervalo de aproximadamente 0,1 mg a aproximadamente 3.500 mg por día. Para un ser humano adulto normal que tiene una masa corporal de aproximadamente 70 kg normalmente es suficiente una dosificación en el intervalo de aproximadamente 0,01 mg a aproximadamente 50 mg por kg de masa corporal, y preferentemente de aproximadamente 0,2 a 2,5 mg por kg, en dosis diarias

únicas o divididas. La administración puede ser en dosis únicas (por ejemplo, una vez al día) o múltiples o mediante infusión constante.

Puede requerirse alguna variabilidad en el intervalo de dosificación general dependiendo de la edad y masa del sujeto que va a tratarse, la vía de administración prevista, el compuesto particular que va a administrarse y similares. La determinación de los intervalos de dosificación y las dosificaciones óptimas para un sujeto mamífero particular está dentro de la capacidad de un experto que tiene el beneficio de la presente descripción.

Los compuestos de fórmula (I) pueden administrarse mediante una variedad de vías de administración convencionales que incluyen por vía oral, bucal, sublingual, ocular, tópica (por ejemplo, transdérmica), parenteral (por ejemplo, intravenosa, intramuscular o subcutánea), rectal, intracisternal, intravaginal, intraperitoneal, intravesical, local (por ejemplo, polvo, pomada o gota), nasal y/o formas farmacéuticas para inhalación o usando una formulación "instantánea", es decir, que permite que la medicación se disuelva en la boca sin la necesidad de usar agua. Como reconocerá un experto en la materia, la pauta posológica de dosificación apropiada, la cantidad de cada dosis administrada y los intervalos entre dosis del compuesto dependerán del compuesto de fórmula (I), o el profármaco del mismo, que va a usarse, el tipo de composiciones farmacéuticas que van a usarse, las características del sujeto que va a tratarse y/o la gravedad de las afecciones que van a tratarse.

Los procedimientos para preparar diversas composiciones farmacéuticas con cantidades de principios activos son conocidos o serán evidentes a la luz de esta descripción para aquellos expertos en esta materia. Véase, por ejemplo, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton,

PA, 19ª Ed. (1995).

Excipientes, vehículos y diluyentes farmacéuticos adecuados para tales composiciones incluyen diluyentes sólidos inertes o cargas, disoluciones acuosas estériles y diversos disolventes orgánicos. Las composiciones farmacéuticas formadas mediante la combinación de un compuesto de esta invención y excipientes, vehículos o diluyentes farmacéuticamente aceptables se administran fácilmente en una variedad de formas farmacéuticas tales como comprimidos, polvos, pastillas para chupar, jarabes, disoluciones inyectables y similares.

Las formas farmacéuticas sólidas para administración por vía oral incluyen cápsulas, comprimidos, polvos y gránulos. En tales formas farmacéuticas sólidas, el compuesto activo se mezcla con al menos un excipiente (o vehículo) farmacéutico convencional inerte tal como citrato de sodio, carbonato cálcico o fosfato dicálcico, o (a) cargas o sustancias de relleno, tales como por ejemplo almidones, lactosa, sacarosa, manitol y ácido silícico; (b) aglutinantes, tales como por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidona, sacarosa y goma arábiga; (c) humectantes, tales como por ejemplo glicerol; (d) agentes de disgregación, tales como por ejemplo agar-agar, carbonato cálcico, almidón de patata o tapioca, ácido algínico, ciertos silicatos complejos y carbonato sódico; (e) retardadores de la disolución, tales como por ejemplo parafina; (f) aceleradores de la absorción, tales como por ejemplo compuestos de amonio cuaternario; (g) agentes mojantes, tales como por ejemplo alcohol cetílico y monoestearato de glicerol; (h) adsorbentes, tales como por ejemplo caolín y bentonita; y/o (i) lubricantes, tales como por ejemplo talco, estearato de calcio, estearato de

magnesio, polietilenglicoles sólidos, lauril sulfato de sodio o mezclas de los mismos. En el caso de cápsulas y comprimidos, las formas farmacéuticas pueden comprender adicionalmente agentes de tamponamiento.

Las formas farmacéuticas sólidas pueden formularse como formas farmacéuticas de liberación modificada y liberación pulsátil que contienen excipientes tales como aquellos detallados anteriormente para las formas farmacéuticas de liberación inmediata junto con excipientes adicionales que actúan como modificadores de la velocidad de liberación, estando estos recubiertos y/o incluidos en el cuerpo del dispositivo. Los modificadores de la velocidad de liberación incluyen, pero no se limitan a, hidroxipropilmetilcelulosa, metilcelulosa, carboximetilcelulosa sódica, etilcelulosa, acetato de celulosa, poli(óxido de etileno), goma xantana, copolímero de metacrilato de amonio, aceite de ricino hidrogenado, cera de carnauba, cera de parafina, acetato ftalato de celulosa, ftalato de hidroxipropilmetilcelulosa, copolímero de ácido metacrílico y mezclas de los mismos. Las formas farmacéuticas de liberación modificada y liberación pulsátil pueden contener uno o una combinación de excipientes modificadores de la velocidad de liberación.

Las composiciones farmacéuticas de la invención pueden comprender adicionalmente formulaciones de dosificación de rápida dispersión o disolución (FDDF). Los términos dispersión o disolución como se usan en este documento para describir FDDF dependen de la solubilidad de la sustancia del fármaco usada, es decir, si la sustancia del fármaco es insoluble, puede prepararse una forma farmacéutica de rápida dispersión, y si la sustancia del fármaco es soluble, puede prepararse una forma farmacéutica de rápida disolución.

Las composiciones sólidas de un tipo similar también pueden emplearse

como cargas en cápsulas de gelatina rellenas blandas o duras que usan tales excipientes como lactosa o azúcar de la leche, además de polietilenglicoles de alto peso molecular y similares.

Las formas farmacéuticas sólidas tales como comprimidos, grageas, cápsulas y gránulos pueden prepararse con recubrimientos y vainas tales como recubrimientos entéricos y otros muy conocidos para un experto en la materia. También pueden comprender agentes opacificantes, y también pueden ser de tal composición que liberen el (los) compuesto(s) activo(s) en un modo retrasado, sostenido o controlado. Ejemplos de composiciones incorporadas que pueden emplearse son sustancias poliméricas y ceras. El (Los) compuesto(s) activo(s) también pueden estar en forma microencapsulada, cuando corresponda, con uno o más de los excipientes anteriormente mencionados.

Las formas farmacéuticas líquidas para administración por vía oral incluyen emulsiones, disoluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Además de los compuestos activos, la forma farmacéutica líquida puede contener diluyente inertes comúnmente usados en la técnica, tales como agua u otros disolventes, agentes solubilizantes y emulsionantes, como por ejemplo etanol, isopropanol, carbonato de etilo, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, aceites (en particular, aceite de algodón, aceite de cacahuete, aceite de germen de maíz, aceite de oliva, aceite de ricino y aceite de semilla de sésamo), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácidos grasos de sorbitano, o mezclas de estas sustancias y similares.

Además del (de los) compuesto(s) activo(s), la composición

farmacéutica puede incluir adicionalmente agentes de suspensión, tales como por ejemplo alcoholes isoestearílicos etoxilados, polioxietilensorbitol y ésteres de sorbitano, celulosa microcristalina, metahidróxido de aluminio, bentonita, agar-agar y tragacanto, o mezclas de estas sustancias y similares. También pueden incluirse edulcorantes, agentes aromatizantes y de perfumado.

Las composiciones farmacéuticas de la invención puede comprender adicionalmente adyuvantes, tales como agentes conservantes, mojantes, emulsionantes y dispersantes. La prevención de la contaminación por microorganismos de las presentes composiciones puede llevarse a cabo con diversos agentes antibacterianos y antifúngicos, por ejemplo, parabenos, clorobutanol, fenol, ácido sórbico y similares. También puede desearse incluir agentes isotónicos, por ejemplo, azúcares, cloruro sódico y similares. La absorción prolongada de composiciones farmacéuticas inyectables puede afectarse por el uso de agentes que pueden retrasar la absorción, por ejemplo monoestearato de aluminio y gelatina.

Para administración parenteral pueden emplearse disoluciones en aceite de sésamo o cacahuete, propilenglicol acuoso o en disoluciones acuosas estériles. Tales disoluciones acuosas deberían estar adecuadamente tamponadas, si fuera necesario, y el diluyente líquido se vuelve en primer lugar isotónico mediante suficiente solución salina o glucosa. Estas disoluciones acuosas son especialmente adecuadas para administración intravenosa, intramuscular, subcutánea e intraperitoneal. A este respecto, todos los medios acuosos estériles empleados están fácilmente disponibles mediante técnicas convencionales conocidas para aquellos expertos en la materia.

Para administración intranasal o administración mediante inhalación, los

compuestos de fórmula (I) se administran convenientemente en forma de una disolución o suspensión a partir de un recipiente pulverizador con bomba que se aprieta o bombea por el paciente o como una presentación de pulverizador de aerosol desde un envase presurizado o nebulizador, con el uso de un propelente adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso de un aerosol presurizado, la unidad de dosificación puede determinarse proporcionando una válvula para administrar una cantidad dosificada. El envase presurizado o nebulizador puede contener una disolución o suspensión de un compuesto de esta invención. Las cápsulas y cartuchos (hechas, por ejemplo, de gelatina) para uso en un inhalador o insuflador pueden formularse conteniendo una mezcla en polvo de un compuesto o compuestos de la invención y una base de polvo adecuada tal como lactosa o almidón.

Las composiciones farmacéuticas de la presente invención también pueden configurarse para tratamientos en uso veterinario, en los que un compuesto de la presente invención, o una sal veterinariamente aceptable del mismo, o solvato o profármaco veterinariamente aceptable del mismo, se administra como una formulación adecuadamente aceptable según la práctica veterinaria normal y el veterinario determinará la pauta posológica de dosificación y la vía de administración que serán más apropiadas para un animal particular.

En general, los compuestos de fórmula (I), y las sales farmacéuticamente aceptables de los mismos, pueden prepararse según las rutas a modo de ejemplo descritas en los esquemas y ejemplos de más adelante, además de mediante otros procedimientos preparativos

convencionales conocidos o evidentes a la luz de la presente descripción para un experto en la materia. Estos procedimientos forman aspectos adicionales de la invención.

Algunos de los compuestos de partida para las reacciones descritas en los esquemas y ejemplos se preparan como se ilustran en este documento. Todos los otros compuestos de partida pueden obtenerse a partir de fuentes comerciales generales, tales como Sigma-Aldrich Corporation, St. Louis, MO.

A menos que se indique lo contrario, las siguientes abreviaturas experimentales tienen los significados indicados:

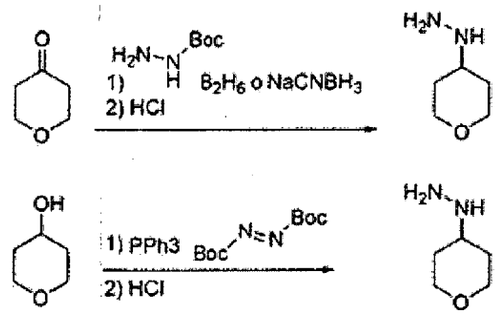
µl - microlitro	M - multiplete
da - doblete ancho	MHz- megahercio
ma - multiplete ancho	min - minuto(s)
BOC - *t*-butoxicarbonilo	MeOH - metanol
sa – singlete ancho	mg - miligramo
$CDCl_3$ - cloroformo deuterado	ml - mililitro
CD_3OD - metanol deuterado	mmol - milimoles
dd - doblete de dobletes	MPLC - cromatografía líquida de media presión
DMF - dimetilformamida	EM - espectroscopía de masas
DMSO - dimetilsulfóxido	RMN - resonancia magnética nuclear
dt - doblete de tripletes	ppm - partes por millón
EtOAc - acetato de etilo	psi - libras por pulgada cuadrada
EtOH - etanol	S - singlete
h (por ejemplo, 1 h, 2 h) - hora(s)	SPA - ensayo de proximidad de

	centelleo
H (por ejemplo, 1H, 2H) - hidrógeno(s)	t - triplete
Hz - hercio	THF - tetrahidrofurano
IPA - alcohol isopropílico	Tris -tris(hidroximetil)aminometano
J - constante de acoplamiento spin-spin	
CL - cromatografía líquida	

Los procedimientos descritos en los presentes esquemas y ejemplos están previstos solamente para fines de ilustración de la presente invención y no deben interpretarse como limitaciones de la misma.

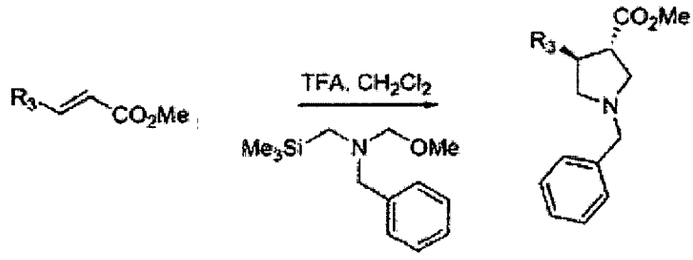
El esquema 1 ilustra múltiples rutas para formar hidrazinas alifáticas que pueden utilizarse para preparar los compuestos de esta patente. Las cetonas pueden convertirse en la imina de hidrazida y reducirse con borano o cianoborohidruro de sodio. También pueden utilizarse otros agentes reductores. A continuación, el grupo boc puede eliminarse con ácido para formar el producto intermedio de hidrazina deseado. Alternativamente, los alcoholes alifáticos pueden convertirse en hidrazinas protegidas por boc mediante tratamiento con trifenilfosfina y diazacarboxilato de di-*t*-butilo. Los grupos boc pueden eliminarse de nuevo con ácido para liberar la hidrazina. La síntesis de hidrazinas aromáticas es muy conocida en la bibliografía mediante la conversión de anilinas en hidrazinas mediante química de diazotización seguida por reducción.

Esquema 1



Los productos intermedios de pirrolidina pueden formarse mediante acoplamiento de ésteres alfa-beta insaturados con N-(metoximetil)(fenil)-N-((trimetilsilil)metil)metanamina que está comercialmente disponible mediante catálisis con ácido. Esta química se ilustra más adelante en la sección experimental y también mediante numerosos ejemplos bibliográficos tales como Hosomi *y col.*, *Chem. Lett.* 13(7) 1117-1120, 1984. Las pirrolidinas también se han sintetizado en un modo enantiomérico puro o empleando auxiliares quirales en el éster (véase Nichols *y col.*, *Org. Lett.,* 8(7), 1495-1498, 2006) o utilizando una bencilamina quiral en la química de cicloadición (véase Haight *y col.*, *Org. Proc. Res. Dev.*, 8(6), 897-902, 2004).

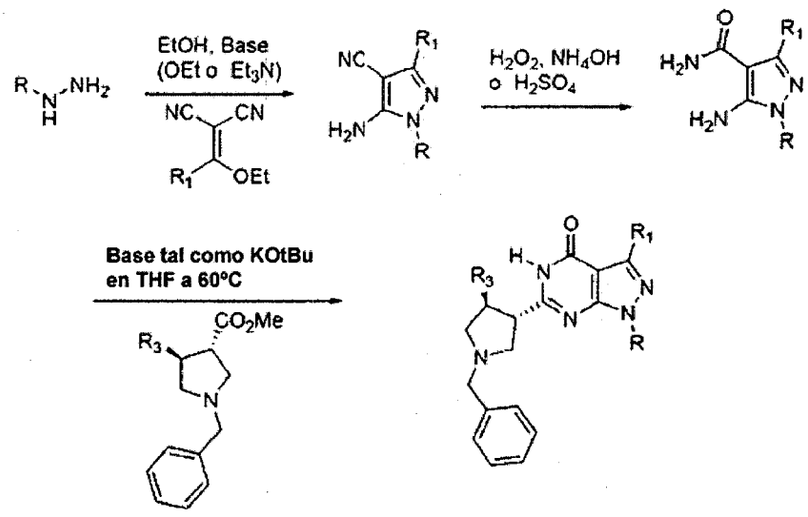
Esquema 2



A continuación, las hidrazinas pueden acoplarse en presencia de una base tal como metóxido de sodio o trietilamina con 2-(etoximetilen)malononitrilo o variantes sustituidas para dar los aminocianopirazoles deseados. El grupo

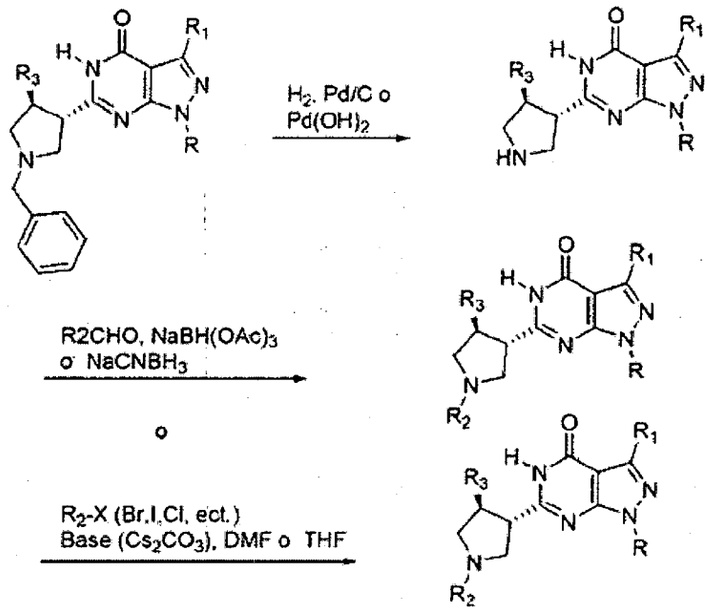
ciano puede oxidarse mediante una variedad de reactivos, pero se han utilizado dos condiciones para preparar los compuestos para esta patente. El ácido sulfúrico concentrado o peróxido de hidrógeno con hidróxido de amonio ha proporcionado los amino-amida-pirazoles. A continuación, los amino-amida-pirazoles pueden acoplarse con ésteres en presencia de una base tal como *t*-butóxido de potasio con calentamiento. El disolvente preferido para esta reacción ha sido tetrahidrofurano y en algunos casos pueden emplearse agentes deshidratantes tales como tamices moleculares para mejorar los rendimientos del acoplamiento.

Esquema 3



A continuación, el grupo bencilo puede eliminarse en condiciones de hidrogenación convencionales para proporcionar la amina secundaria que está lista para posterior funcionalización. La amina puede alquilarse con haluros de alquilo en presencia de base o química de aminación reductora utilizando una variedad de agentes reductores de tipo hidruro pueden proporcionar los compuestos deseados.

Esquema 4

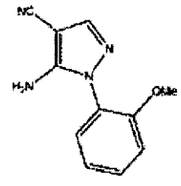


EJEMPLOS

Los ejemplos siguientes están previstos para ilustrar realizaciones particulares de la invención y preparaciones de la misma y no pretenden limitar en ningún modo la memoria descriptiva, incluyendo las reivindicaciones. A menos que se indique lo contrario, todos los reactivos empleados se obtuvieron comercialmente.

EJEMPLO 1

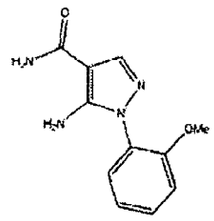
(a) 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo



A una disolución de clorhidrato de 1-(2-metoxifenil)hidrazina (3 g, 0,017 mol) en etanol (50 ml) se añadió 2-(metoximetilen)malononitrilo (1,89 g, 0,9 eq)

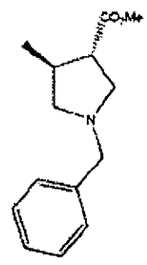
y metóxido de sodio (1,92 g, 2,1 eq). La mezcla de reacción se calentó a reflujo durante 18 h y se concentró. La mezcla de reacción se repartió entre salmuera y acetato de etilo. La fase orgánica se separó, se secó con sulfato de magnesio, se filtró y se concentró. La cromatografía MPLC en Biotage eluyendo con 20-60% de acetato de etilo/hexanos dio el compuesto del título en 53% de rendimiento (1,9 g). 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,64 (m, 1H), 7,40 (m, 2H), 7,08 (m, 2H), 4,51 (sa, 2H), 3,87 (s, 3H); EM: (M^+H m/z = 215,2).

(b) 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida



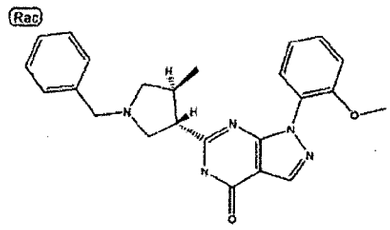
A una disolución de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo (1,53 g) en hidróxido de amonio saturado (30 ml) se añadió una disolución de peróxido de hidrógeno al 30% (6 ml). La reacción se agitó durante 18 h a temperatura ambiente y se inactivó lentamente con 60 ml de una disolución saturada de sulfato de sodio. La fase acuosa se extrajo con acetato de etilo, se secó con sulfato de magnesio, se filtró y se concentró. La cromatografía MPLC en Biotage eluyendo con 2-6% de metanol/cloruro de metileno proporcionó 1,38 g (84%) del compuesto del título. 400 MHz RMN ^{1}H (DMSO) δ 7,79 (s, 1H), 7,42 (m, 1H), 7,25 (d, *J*= 7,5 Hz, 2H), 7,19 (d, *J*= 8,3 Hz, 2H), 7,03 (t, *J*= 6,2 Hz, 1H), 5,83 (s, 2H), 3,76 (s, 3H); EM: (M^+H m/z = 233,2).

(c) (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo



A una disolución de (E)-but-2-enoato de metilo (1,6 g) se añadió tolueno (30 ml), N-(metoximetil)(fenil)-N-((trimetilsilil)metil)metanamina (3,7 g) y ácido trifluoroacético (1,5 g). La mezcla de reacción se calentó a 50ºC durante 18 h. La mezcla de reacción se concentró, se inactivó con bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía MPLC eluyendo con 20-30% de acetato de etilo/hexanos proporcionó el compuesto del título (1,5 g). 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,33-7,20 (m, 5H), 4,15-4,08 (m, 1H), 3,66-3,53 (m, 2H), 2,87-2,74 (m, 2H), 2,53-2,44 (m, 2H), 2,23-2,19 (m, 1H), 1,23 (t, *J*= 7,1 Hz, 3H), 1,11 (d, *J*= 6,6 Hz, 3H).

(d) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

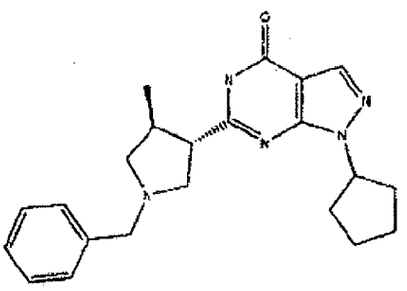


A (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo (241 mg) y 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida (200 mg) se añadió una disolución de *t*-butóxido de potasio (1 M) en THF (4,31 ml, 5 eq). La mezcla de reacción se calentó a reflujo durante 16 h y se vertió sobre bicarbonato sódico

saturado. La fase acuosa se extrajo con acetato de etilo, se secó con sulfato de magnesio, se filtró y se concentró. La cromatografía MPLC en Biotage eluyendo con 1-4% de metanol/cloruro de metileno con 0,5% de hidróxido de amonio saturado proporcionó 79 mg del compuesto del título. 400 MHz RMN ^{1}H (DMSO) δ 8,16 (d, *J*= 7,9 Hz, 1H), 7,92 (s, 1H), 7,34 (m, 5H), 7,09 (m, 1H), 6,92 (m, 2H), 3,89 (s, 3H), 3,84 (m, 1H), 3,71 (m, 1H), 3,37 (t, *J*= 9,1 Hz, 1H), 3,09 (m, 1H), 2,85 (m, 1H), 2,65 (m, 1H), 2,47 (m, 1H), 2,03 (m, 2H), 1,19 (d, *J*= 7,1 Hz, 3H); EM: (M^+H m/z = 416,1).

EJEMPLO 2

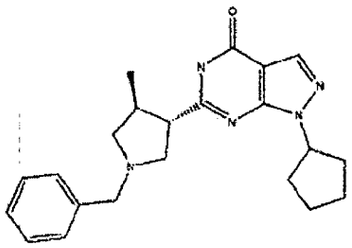
6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H (CD_3OD) δ 8,00 (s, 1H), 7,38-7,23 (m, 5H), 5,14-5,10 (m, 1H), 3,80-3,57 (m, 2H), 3,34 (t, *J*= 8,3 Hz, 1H), 2,97 (d, *J*= 9,9 Hz, 1H), 2,80-2,78 (m, 1H), 2,53-2,49 (m, 1H), 2,41-2,38 (m, 1H), 2,10-1,89 (m, 7H), 1,70-1,66 (m, 2H), 1,17 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 378,1).

EJEMPLO 3

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

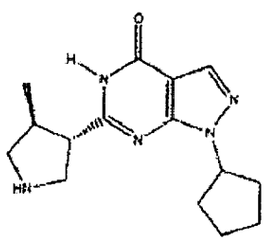


El racemato se separó en una columna de HPLC quiral Chiralcel OD, fase móvil 90/10 heptano/EtOH, t_R = 6,807, para proporcionar el enantiómero. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,38-7,22 (m, 5H), 5,27-5,10 (m, 1H), 3,78 (d, *J*= 12,5 Hz, 1H), 3,6 (d, *J*= 12,5 Hz, 1H), 3,34 (t, *J*= 8,3 Hz, 1H), 2,97 (d, *J*= 9,9 Hz, 1H), 2,80-2,78 (m, 1H), 2,52-2,48 (m, 1H), 2,41-2,38 (m, 1H), 2,10-1,89 (m, 7H), 1,70-1,66 (m, 2H), 1,18 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 378,1).

Chiralcel OD, fase móvil 90/10 heptano/IPA, t_R = 9,433.

EJEMPLO 4

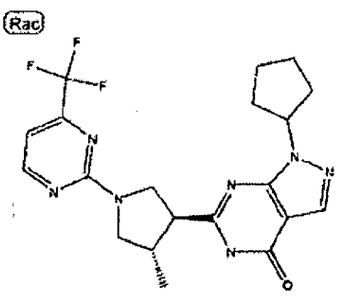
(a) 1-ciclopentil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



Una disolución de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona (970 mg) en 25 ml de etanol se añadió a una botella Parr. Se añadió ácido acético (2,5 ml) y $Pd(OH)_2$

(500 mg). La mezcla de reacción se colocó en un hidrogenador a 40 psi (276 KPa) durante 16 h. La mezcla de reacción se filtró a través de Celite y se concentró. La mezcla de reacción se repartió entre disolución saturada de bicarbonato y cloruro de metileno. Las fases se separaron y la fase acuosa se extrajo 6x con cloruro de metileno. La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró para proporcionar 429 mg del compuesto del título. 400 MHz RMN ^{1}H (CD_3OD) δ 9,25 (sa, 1H), 8,02 (s, 1H), 5,20-5,17 (m, 1H), 3,91 (m, 1H), 3,77-3,68 (m, 2H), 3,46-3,44 (m, 1H), 3,10 (m, 1H), 2,89 (m, 1H), 2,13-1,87 (m, 6H), 1,74-1,65 (m, 2H), 1,20 (d, *J*= 6,2 Hz, 3H). EM: (M^+H m/z = 288,1).

(b) 1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(trifluorometil)pirimidin-2-il]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

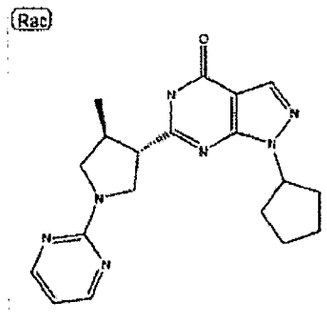


A una disolución de 1-ciclopentil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (40 mg) en dimetilformamida (1 ml) se añadió carbonato de cesio (2 eq) y 2-cloro-4-(trifluorometil)pirimidina (1,2 eq) y la mezcla de reacción se calentó a 60°C durante 90 min. La mezcla de reacción se vertió sobre bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía MPLC en Biotage eluyendo con 20-60% de acetato de etilo/hexanos proporcionó 40 mg del compuesto del título. 400 MHz RMN ^{1}H

($CDCl_3$) δ 8,51 (d, *J*= 5,0 Hz, 1H), 8,02 (m, 1H), 6,79 (d, *J*= 4,6 Hz, 1H), 5,16-5,08 (m, 1H), 4,24-3,97 (m, 3H), 3,37-3,32 (m, 1H), 3,20-3,14 (m, 1H), 2,09-2,05 (m, 3H), 1,96-1,90 (m, 1H), 1,73-1,56 (m, 5H), 1,24 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 434,1).

EJEMPLO 5

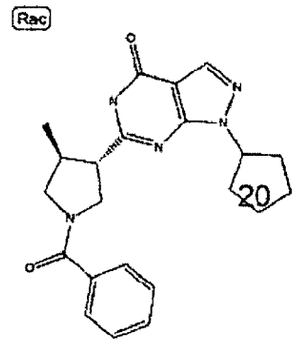
1-ciclopentil-6-[(3,4-trans)-4-metil-1-pirimidin-2-ilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(trifluorometil)pirimidin-2-il]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 2-cloropirimidina. 400 MHz RMN ^1H (CD_3OD) δ 8,29 (d, *J*= 5,0 Hz, 2H), 7,96 (s, 1H), 6,60 (t, *J*= 5,0 Hz, 1H), 5,08-5,04 (m, 1H), 4,06-3,87 (m, 3H), 3,23-3,18 (m, 1H), 3,12 (q, *J*= 7,9 Hz, 1H), 2,80-2,76 (m, 1H), 2,05-1,98 (m, 4H), 1,90-1,82 (m, 2H), 1,66-1,61 (m, 2H), 1,17 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 366,1).

EJEMPLO 6

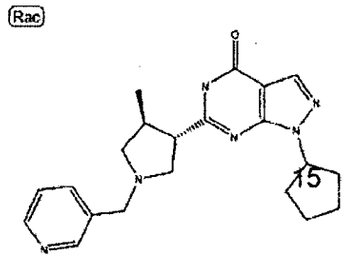
6-[(3,4-trans)-1-benzoil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de 1-ciclopentil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (40 mg) en cloruro de metileno (1 ml) se añadió trietilamina (2,5 eq) y cloruro de benzoílo (1,2 eq) y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se vertió sobre bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La cromatografía MPLC en Biotage eluyendo con 2-4% de metanol/cloruro de metileno proporcionó el compuesto del título (27 mg). 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,06-8,03 (m, 1H), 7,57-7,50 (m, 2H), 7,43-7,37 (m, 3H), 5,20-5,13 (m, 1H), 4,16-4,03 (m, 1H), 3,92 (d, *J*= 8,3 Hz, 1H), 3,81-3,76 (m, 1H), 3,47-3,29 (m, 1H), 3,17-3,03 (m, 1H), 2,84-2,67 (m, 1H), 2,11-1,80 (m, 3H), 1,79-1,72 (m, 1H), 1,56-1,30 (m, 4H), 1,21-1,11 (m, 3H). EM: (M^+H m/z = 392,1).

EJEMPLO 7

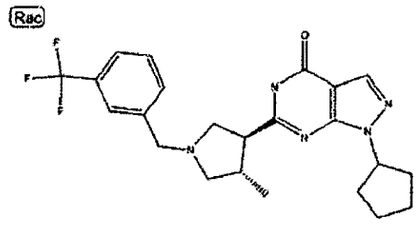
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de 1-ciclopentil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (40 mg) en 1,2-dicloroetano (2 ml) se añadió ácido acético (2 eq), nicotinaldehído (1,5 eq) y triacetoxiborohidruro de sodio (58 mg). La mezcla de reacción se calentó a 40ºC durante 4 h, se vertió sobre bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía MPLC en Biotage eluyendo con 1-4% de metanol/cloruro de metileno/0,5% de hidróxido de amonio proporcionó el compuesto del título (47 mg). 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,55 (m, 2H), 2,02 (s, 1H), 7,84 (m, 1H), 7,36 (m, 1H), 5,16-5,09 (m, 1H), 3,82-3,60 (m, 2H), 3,36 (m, 1H), 3,05-2,38 (m, 4H), 2,13-1,89 (m, 7H), 1,73-1,68 (m, 2H), 1,21 (m, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 379,1).

EJEMPLO 8

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[3-(trifluorometil)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

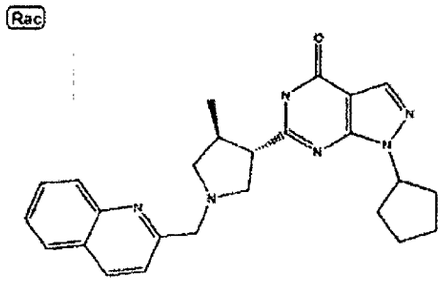


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 3-(trifluorometil)benzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,66 (s, 1H), 7,53-7,50 (m, 3H), 5,16-5,09 (m, 1H), 3,80 (m, 1H), 3,69-3,66 (m, 1H), 3,35 (m, 1H), 2,99 (m, 1H), 2,83 (m, 1H), 2,42 (m, 1H), 2,12-1,93 (m, 7H), 1,74-1,68 (m, 2H), 1,56 (m, 1H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 446,0).

EJEMPLO 9

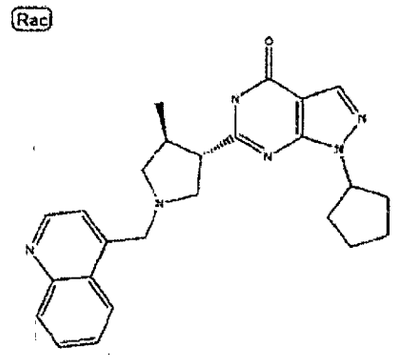
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,22-8,15 (m, 2H), 8,07 (s, 1H), 7,80 (d, *J*= 7,9 Hz, 1H), 7,71 (t, *J*= 8,3 Hz, 1H), 7,69-7,50 (m, 2H), 5,18-5,11 (m, 1H), 4,25 (m, 1H), 3,91 (m, 1H), 3,71 (m, 1H), 3,49 (m, 1H), 3,17 (m, 1H), 2,87 (m, 1H), 2,73-2,45 (m, 2H), 2,13-1,94 (m, 6H), 1,75-1,68 (m, 2H), 1,23 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 429,1).

EJEMPLO 10

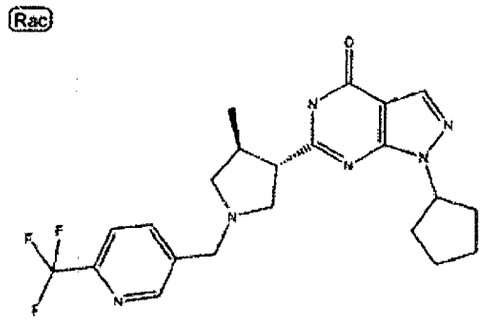
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,92-8,89 (m, 1H), 8,27-8,25 (m, 1H), 8,18-8,16 (m, 1H), 8,00 (s, 1H), 7,80-7,74 (m, 2H), 7,63-7,50 (m, 1H), 5,14-5,07 (m, 1H), 4,18 (m, 2H), 3,37 (m, 1H), 3,10-2,30 (m, 5H), 2,15-1,93 (m, 6H), 1,74-1,64 (m, 2H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 429,1).

EJEMPLO 11

1-ciclopentil-6-[(3,4-trans)-4-metil-1-{[6-(trifluorometil)piridin-3-il]metil}pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

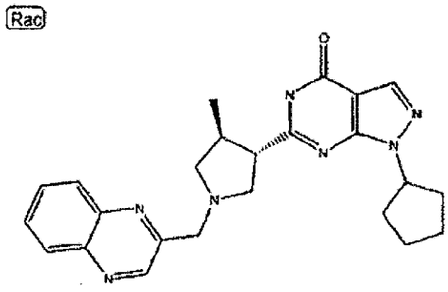


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-

(trifluorometil)nicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,63 (m, 1H), 8,01 (s, 1H), 7,7 (d, *J*= 7,80 Hz, 1H), 5,12 (m, 1H), 4,82 (m, 1H), 3,79 (q, *J*= 13,2, 16,2, Hz, 2H), 3,32 (t, *J*= 8,5 Hz, 1H), 3,02 (m, 1H), 2,86 (m, 1H), 2,63 (m, 1H), 2,45 (m, 1H), 2,12-2,88 (m, 6H), 1,74-1,64 (m, 3H), 1,32 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 447,0).

EJEMPLO 12

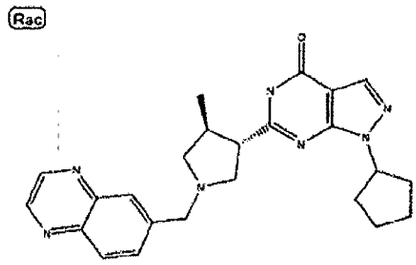
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinoxalin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinoxalin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,86 (s, 1H), 8,31-8,29 (m, 1H), 8,05-8,08 (m, 2H), 7,79-7,70 (m, 2H), 5,16-5,12 (m, 1H), 4,32-4,28 (m, 1H), 3,94-3,98 (m, 1H), 3,46 (t, *J*= 8,3 Hz, 1H), 3,26 (d, *J*= 9,5 Hz, 1H), 2,90-2,88 (m, 1H), 2,64-2,60 (m, 1H), 2,50-2,47 (m, 1H), 2,18 (t, *J*= 8,3 Hz, 1H), 2,11-1,91 (m, 6H), 1,71-1,66 (m, 2H), 1,23 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 430,1).

EJEMPLO 13

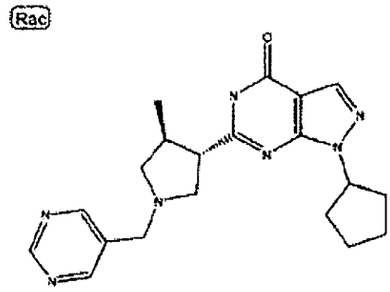
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,82 (s, 2H), 8,14 (d, *J*= 8,3 Hz, 1H), 8,07-7,93 (m, 3H), 5,15-5,08 (m, 1H), 4,00-3,87 (m, 2H), 3,37 (t, *J*= 8,7 Hz, 1H), 3,04 (d, *J*= 9,5 Hz, 1H), 2,85-2,84 (m, 1H), 2,66-2,62 (m, 1H), 2,46-2,42 (m, 1H), 2,11-1,92 (m, 7H), 1,71-1,63 (m, 2H), 1,20 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 430,1).

EJEMPLO 14

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(pirimidin-5-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

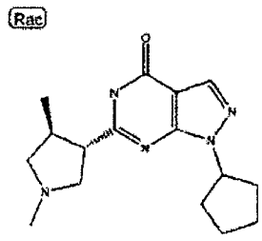


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por pirimidin-5-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 9,16 (s, 1H), 8,76 (s, 2H),

8,02 (s, 1H), 5,17-5,10 (m, 1H), 3,78-3,69 (m, 2H), 3,27 (t, *J*= 8,7 Hz, 1H), 3,07 (d, *J*= 9,5 Hz, 1H), 2,89 (m, 1H), 2,69 (m, 1H), 2,48-2,46 (m, 1H), 2,12-1,89 (m, 6H), 1,74-1,63 (m, 3H), 1,26-1,19 (m, 3H). EM: (M^+H m/z = 380,1).

EJEMPLO 15

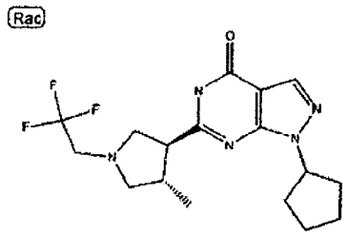
1-ciclopentil-6-[(3,4-trans)-1,4-dimetilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por formaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 8,04 (s, 1H), 5,18-5,11 (m, 1H), 3,39 (m, 1H), 3,15 (m, 1H), 3,03-2,96 (m, 1H), 2,70 (m, 1H), 2,51 (m, 4H), 2,15-1,90 (m, 7H), 1,75-1,66 (m, 2H), 1,20 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 302,2).

EJEMPLO 16

1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2,2,2-trifluoroetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

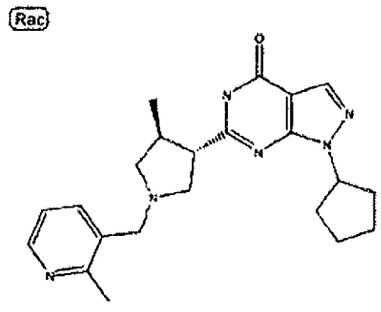


A una disolución de 1-ciclopentil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-

pirazolo[3,4-d]pirimidin-4(5H)-ona (40 mg) en dimetilformamida (1,5 ml) se añadió carbonato sódico (30 mg) y 1,1,1-trifluoro-2-yodoetano (1,1 eq). La mezcla de reacción se calentó a 40ºC durante 3 días. Se añadieron 3 eq adicionales de 1,1,1-trifluoro-2-yodoetano junto con carbonato de cesio (2 eq) y la mezcla de reacción se calentó a 60ºC durante 3 días. La mezcla de reacción se vertió sobre bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante MPLC en Biotage eluyendo con 0,5-2% de metanol/cloruro de metileno/0,5% de hidróxido de amonio proporcionó el compuesto del título (9 mg). 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,03 (s, 1H), 5,16-5,10 (m, 1H), 3,50-3,48 (m, 1H), 3,30-3,25 (m, 2H), 2,52 (m, 1H), 2,25 (m, 1H), 2,13-1,94 (m, 5H), 1,72-1,57 (m, 6H), 1,22 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 370,1).

EJEMPLO 17

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpiridin-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

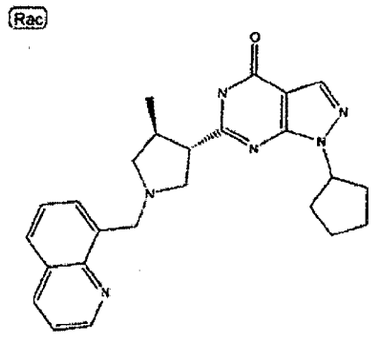


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 2-metilnicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,40-8,39 (m, 1H), 7,99 (s,

1H), 7,62-7,60 (m, 1H), 7,12-7,09 (m, 1H), 5,15-5,08 (m, 1H), 3,73-3,65 (m, 2H), 3,30 (t, *J*= 8,7 Hz, 1H), 3,04 (d, *J*= 9,95 Hz, 1H), 2,86-2,84 (m, 1H), 2,66-2,62 (m, 4H), 2,46-2,39 (m, 1H), 2,11-1,89 (m, 7H), 1,71-1,64 (m, 2H), 1,19 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 393,2).

EJEMPLO 18

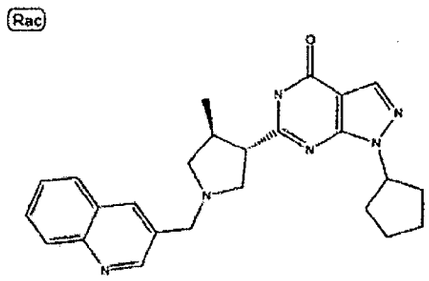
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-8-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-5-carbaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 9,10-9,09 (m, 1H), 8,13 (dd, *J*= 8,3, 1,6 Hz, 1H), 7,98 (s, 1H), 7,76-7,74 (d, *J*= 7,88 Hz, 2H), 7,50 (t, *J*= 7,88 Hz, 1H), 7,45-7,42 (m, 1H), 5,14-5,07 (m, 1H), 4,52 (d, *J*= 12,40 Hz, 1H), 4,21 (d, *J*= 12,40 Hz, 1H), 3,34 (t, *J*= 8,3 Hz, 1H), 3,1 (d, *J*= 9,95 Hz, 1H), 2,8-2,79 (m, 1H), 2,71-2,67 (m, 1H), 2,37-2,31 (m, 1H), 2,10-1,88 (m,7H), 1,72-1,62 (m, 2H), 1,17 (d, *J*= 6,64 Hz, 3H). EM: (M^+H m/z = 429,2).

EJEMPLO 19

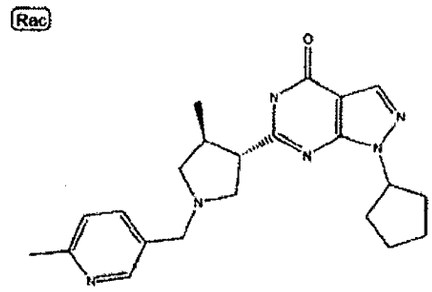
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-3-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,87 (s, 1H), 8,29 (s, 1H), 8,07 (d, *J*= 7,8 Hz, 1H), 8,02 (s, 1H), 7,89 (d, *J*= 7,9 Hz, 1H), 7,70-7,66 (m, 1H), 7,54 (t, *J*= 7,5 Hz, 1H), 5,16-5,08 (m, 1H), 4,02-3,98 (m, 1H), 3,86-3,83 (m, 1H), 3,47 (s, 1H), 3,40 (t, *J*= 8,3 Hz, 1H), 3,07 (d, *J*= 8,5 Hz, 1H), 2,85 (m, 1H), 2,65-2,61 (m, 1H), 2,47-2,46 (m, 1H), 2,15-1,87 (m, 6H), 1,73-1,63 (m, 2H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 429,2).

EJEMPLO 20

1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(6-metilpiridin-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

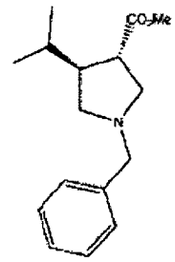


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-

3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-metilnicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,37 (d, *J*= 1,2 Hz, 1H), 8,00 (s, 1H), 7,73 (dd, J= 7,9, 2,1 Hz, 1H), 7,18 (d, *J*= 8,3 Hz, 1H), 5,16-5,08 (m, 1H), 3,76-3,72 (m, 1H), 3,61-3,57 (m, 1H), 3,32 (t, *J*= 8,71 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,83-2,81 (m, 1H), 2,57-2,51 (m, 4H), 2,42-2,38 (m, 1H), 2,11-1,89 (m, 7H), 1,72-1,64 (m, 2H), 1,19 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 393,2).

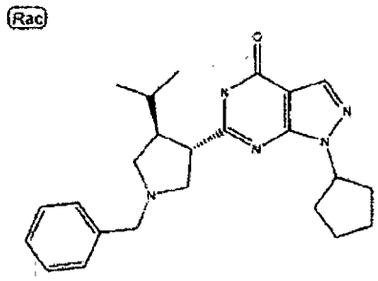
EJEMPLO 21

(a) (3,4-trans)-1-bencil-4-isopropilpirrolidin-3-carboxilato de metilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo, pero sustituyendo por (E)-4-metilpent-2-enoato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,31-7,20 (m, 5H), 3,66 (s, 3H), 3,62-3,49 (m, 2H), 2,79-2,69 (m, 3H), 2,31-2,27 (m, 2H), 1,61-1,56 (m, 1H), 1,27-4,25 (m, 1H), 0,86 (t, *J*= 2,9 Hz, 6H). EM: (M^+H m/z = 262,2).

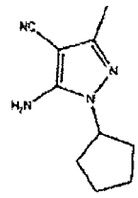
(b) 6-[(3,4-trans)-1-bencil-4-isopropilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-isopropilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,38-7,32 (m, 4H), 7,27-7,24 (m, 1H), 5,13-5,05 (m, 1H), 3,78 (d, *J*= 12,5 Hz, 1H), 3,6 (d, *J*= 12,5 Hz, 1H), 3,27-3,21 (m, 1H), 2,98-2,96 (m, 2H), 2,37 (m, 1H), 2,10-1,88 (m, 7H), 1,69-1,60 (m, 3H), 0,98 (d, *J*= 6,6 Hz, 3H), 0,86 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 406,1).

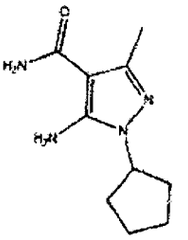
EJEMPLO 22

(a) 5-amino-1-ciclopentil-3-metil-1H-pirazol-4-carbonitrilo



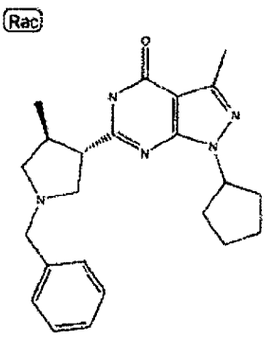
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-ciclopentilhidrazina y 2-(1-metoxietiliden)malononitrilo. RMN ^{1}H (300 MHz, $CDCl_3$): δ 4,24 (m, 3H), 2,24 (s, 3H), 2,01 (m, 4H), 1,90 (m, 2H), 1,67 (m, 2H).

(b) 5-amino-1-ciclopentil-3-metil-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida pero sustituyendo por 5-amino-1-ciclopentil-3-metil-1H-pirazol-4-carbonitrilo. RMN ^{1}H (300 MHz, $CDCl_3$): δ 5,39 (a, 2H), 5,32 (a, 2H), 4,26 (m, 1H), 2,38 (s, 3H), 2,04 (m, 4H), 1,9 (m, 2H), 1,66 (m, 2H).

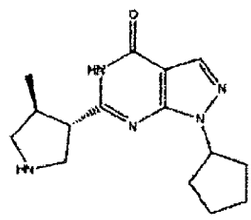
(c) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-3-metil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-3-metil-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,45-7,20 (m, 5H), 5,13-4,96 (m, 1H), 3,85-3,61 (m, 2H), 3,45-3,30 (m, 1H), 3,08-2,98 (m, 1H), 2,82-2,74 (m, 1H), 2,60-2,45 (m, 4H), 2,45-2,30 (m, 1H), 2,18-1,80 (m, 6H), 1,79-1,50 (m, 3H), 1,2-1,1 (m, 3H). EM: (M^+H m/z = 392,5).

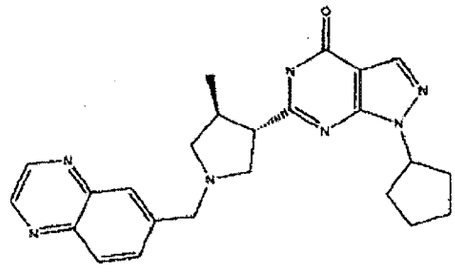
EJEMPLO 23

(a) 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



Una disolución de 6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona (9,25 g) en 100 ml de etanol se añadió a una botella de Parr. Se añadieron 2 ml de HCl concentrado seguido por 3 g de hidróxido de paladio. La mezcla de reacción se colocó en un hidrogenador a 45 psi (310,5 KPa) de gas H_2 durante 4 h. La mezcla de reacción se filtró a través de Celite y se concentró para proporcionar el compuesto del título como una sal de HCl. 400 MHz RMN ^1H ($CDCl_3$) δ 8,00 (s, 1H), 5,14-5,10 (m, 1H), 4,89-3,84 (m, 1H), 3,72-3,67 (m, 1H), 3,38-3,31 (m, 1H), 3,03-2,98 (m, 1H), 2,85-2,81 (m, 1H), 2,08-1,85 (m,7H), 1,69-1,61 (m, 2H), 1,19-1,10 (m, 3H). EM: (M^+H m/z = 288,2).

(b) 1-ciclopentil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

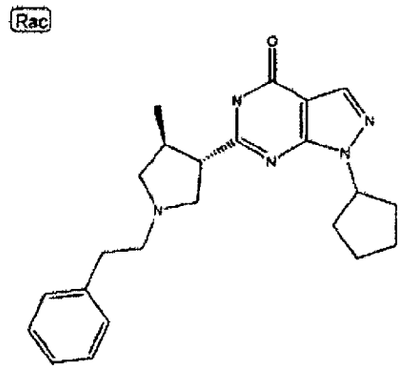


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,82 (s, 2H), 8,14 (d, *J*= 8,3 Hz, 1H), 8,07-7,93 (m, 3H), 5,15-5,08 (m, 1H), 4,00-3,87 (m, 2H), 3,37 (t, *J*= 8,7 Hz, 1H), 3,04 (d, *J*= 9,5 Hz, 1H), 2,85-2,84 (m, 1H), 2,66-2,62 (m, 1H), 2,46-2,42 (m, 1H), 2,11-1,92 (m, 7H), 1,71-1,63 (m, 2H), 1,20 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 430,1).

EJEMPLO 24

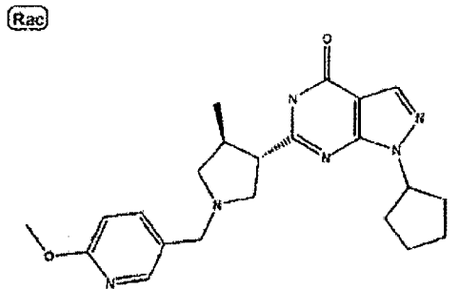
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-feniletil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 2-fenilacetaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,03 (s, 1H), 7,32-7,19 (m, 5H), 5,18-5,11 (m, 1H), 3,44 (t, *J*= 8,7 Hz, 1H), 3,14 (d, *J*= 9,9 Hz, 1H), 2,90-2,78 (m, 5H), 2,56-2,52 (m, 1H), 2,40-2,39 (m, 1H), 2,14-1,89 (m, 7H), 1,73-1,67 (m, 2H), 1,19 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 392,1).

EJEMPLO 25

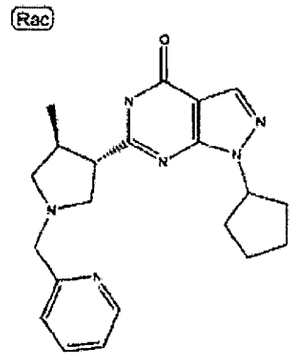
1-ciclopentil-6-{(3,4-trans)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-metoxinicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (dd, *J*= 31,5, 2,5 Hz, 1H), 8,00 (s, 1H), 7,69 (dd, J= 8,3, 2,5 Hz, 1H), 6,76 (d, *J*= 8,3 Hz, 1H), 5,16-5,09 (m, 1H), 3,90 (s, 3H), 3,68 (d, *J*= 12,9 Hz, 1H), 3,55 (d, *J*= 12,9 Hz, 1H), 3,31 (t, *J*= 8,7 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,81-2,79 (m, 1H), 2,54-2,50 (m, 1H), 2,41-2,36 (m, 1H), 2,12-1,87 (m, 7H), 1,73-1,64 (m, 2H), 1,18 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 409,1).

EJEMPLO 26

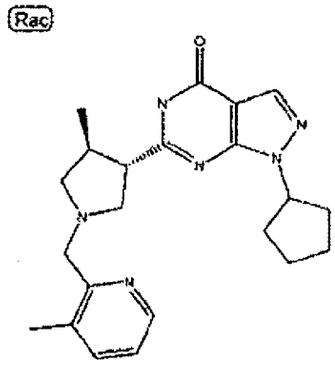
1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por picolinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,63-8,62 (m, 1H), 8,02 (s, 1H), 7,72-7,67 (m, 1H), 7,41 (d, *J*= 7,9 Hz, 1H), 7,20-7,17 (m, 1H), 5,18-5,10 (m, 1H), 4,03 (d, *J*= 13,7 Hz, 1H), 3,75 (d, *J*= 13,7 Hz, 1H), 3,41 (t, *J*= 8,3 Hz, 1H), 3,07 (d, *J*= 9,9 Hz, 1H), 2,83-2,82 (m, 1H), 2,58 (m, 1H), 2,46-2,40 (m, 1H), 2,13-1,89 (m,7H), 1,74-1,64 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 379,1).

EJEMPLO 27

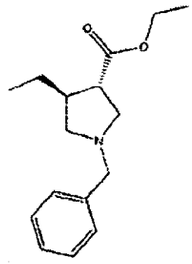
1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(3-metilpiridin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 3-metilpicolinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,57 (t, *J*= 7,5, 1H), 7,22 (d, *J*= 7,8 Hz, 1H), 7,02 (d, *J*= 7,5 Hz, 1H), 5,17-5,09 (m, 1H), 3,97 (d, *J*= 13,3 Hz, 1H), 3,68 (d, *J*= 13,3 Hz, 1H), 3,42 (t, *J*= 8,3 Hz, 1H), 3,05 (d, *J*= 9,9 Hz, 1H), 2,82-2,80 (m, 1H), 2,57-2,53 (m, 1H), 5,54 (s, 3H), 2,44-2,38 (m, 1H), 2,12-1,89 (m, 7H), 1,72-1,64 (m, 2H), 1,19 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 393,1).

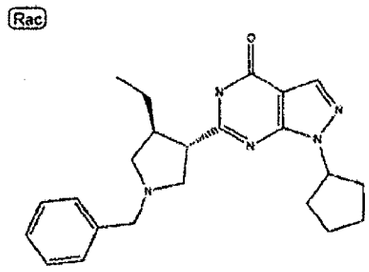
EJEMPLO 28

(a) (3,4-trans)-1-bencil-4-etilpirrolidin-3-carboxilato de etilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo, pero sustituyendo por (E)-pent-2-enoato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,33-7,19 (m, 5H), 4,15-4,08 (m, 2H), 3,65-3,52 (m, 2H), 2,82-2,71 (m, 3H), 2,60-2,55 (m, 1H), 2,38-2,24 (m, 2H), 1,59-1,50 (m, 1H), 1,47-1,38 (m, 1H), 1,23 (t, *J*= 7,5 Hz, 3H), 0,87 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 262,2).

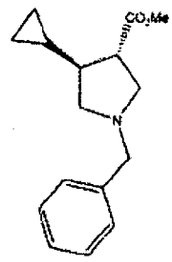
(b) 6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-etilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,39-7,24 (m, 5H), 5,13-5,07 (m, 1H), 3,78 (d, *J*= 13,3 Hz, 1H), 3,58 (d, *J*= 12,9 Hz, 1H), 3,42 (t, *J*= 12,9 Hz, 1H), 3,33 (t, *J*= 8,7 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,86 (m, 1H), 2,46-2,42 (m, 1H), 2,19-1,44 (m, 11H), 0,92 (t, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 392,1).

EJEMPLO 29

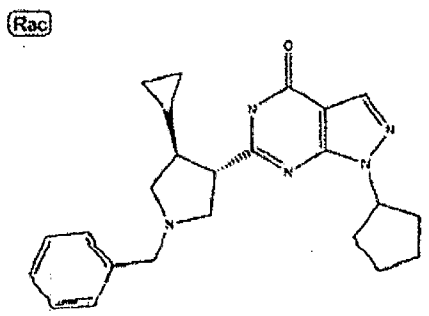
(a) (3,4-trans)-1-bencil-4-ciclopropilpirrolidin-3-carboxilato de metilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo pero sustituyendo por (E)-3-ciclopropilacrilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,33-7,20 (m, 5H), 3,66 (s, 3H), 3,64-3,54 (m, 2H), 2,87-2,81 (m, 2H),

2,77-2,70 (m, 2H), 2,47-2,43 (m, 1H), 1,84-1,78 (m, 1H), 0,87-0,79 (m, 1H), 0,45-0,36 (m, 2H), 0,20-0,06 (m, 2H). EM: (M^+H m/z = 260,2).

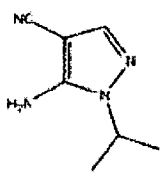
(b) 6-[(3,4-trans)-1-bencil-4-ciclopropilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-ciclopropilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^1H ($CDCl_3$) δ 7,99 (s, 1H), 7,38-7,31 (m, 4H), 7,27-7,23 (m, 1H), 5,14-5,10 (m, 1H), 3,78 (d, *J*= 12,4 Hz, 1H), 3,63 (d, *J*= 12,4 Hz, 1H), 3,32 (t, *J*= 8,7 Hz, 1H), 3,12-3,10 (m, 1H), 3,01 (d, *J*= 9,9 Hz, 1H), 2,59-2,57 (m, 1H), 2,20-1,87 (m, 8H), 1,71-1,65 (m, 2H), 0,86-0,84 (m, 1H), 0,52-0,48 (m, 2H), 0,19-0,09 (m, 2H). EM: (M^+H m/z = 393,1).

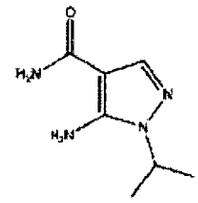
EJEMPLO 30

(a) 5-amino-1-isopropil-1H-pirazol-4-carbonitrilo



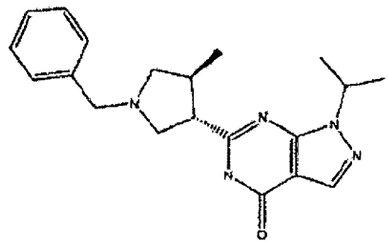
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-isopropilhidrazina. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,50 (s, 1H), 4,22-4,16 (m, 3H), 1,45 (d, *J*= 6,6 Hz, 6H). EM: (M^+H m/z = 151,1).

(b) 5-amino-1-isopropil-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-1-isopropil-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,67 (s, 1H), 4,40-4,33 (m, 1H), 1,37 (d, *J*= 6,6 Hz, 6H). EM: (M^+H m/z = 169,1).

(c) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

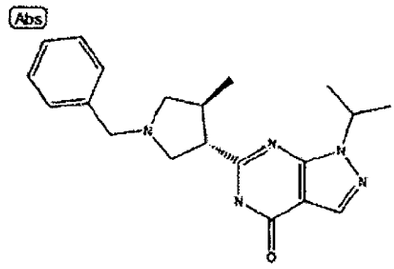


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-isopropil-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,98 (s, 1H), 7,38-7,22 (m, 5H), 5,07-5,04 (m, 1H), 3,77-3,64 (m, 2H), 3,12-3,08 (m, 1H),

2,99-2,91 (m, 3H), 2,67-2,63 (m, 1H), 2,27-2,25 (m, 1H), 1,48 (d, *J*= 7,1 Hz, 6H), 1,14 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 352,1).

EJEMPLO 31

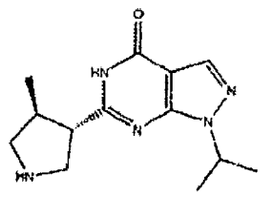
6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El racemato se separó en una columna de HPLC quiral Chiralcel OD, fase móvil 90/10 heptano/EtOH, t_R = 8,917, para proporcionar el enantiómero. 400 MHz RMN ^1H (CD_3OD) δ 7,98 (s, 1H), 7,38-7,33 (m, 2H), 7,33-7,29 (m, 2H), 7,26-7,22 (m, 1H), 5,07-5,02 (m, 1H), 3,77-3,64 (m, 2H), 3,12-3,07 (m, 1H), 2,99-2,91 (m, 3H), 2,67-2,63 (m, 1H), 2,29-2,25 (m, 1H), 1,48 (d, *J*= 6,6 Hz, 6H), 1,14 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 352,1).

EJEMPLO 32

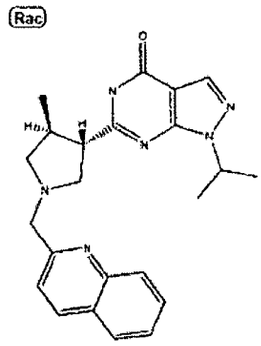
(a) 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-

d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H (CD_3OD) δ 8,02 (s, 1H), 5,11-5,08 (m, 1H), 3,80-3,74 (m, 2H), 3,64-3,57 (m, 1H), 3,30-3,22 (m, 1H), 3,07-3,02 (m, 1H), 2,75-2,71 (m, 1H), 1,49 (dd, *J*= 6,6, 1,7 Hz, 6H), 1,15 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 262,2).

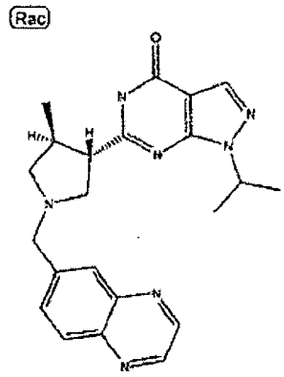
(b) 1-isopropil-6-[(3,4-trans)-4-metil-1-(quinolin-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinolin-2-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,31 (d, *J*= 8,7 Hz, 1H), 8,02 (d, *J*= 8,7 Hz, 1H), 7,98 (s, 1H), 7,95 (d, *J*= 7,9 Hz, 1H), 7,75-7,68 (m, 2H), 7,58-7,54 (m, 1H), 5,07-5,04 (m, 1H), 4,11-3,96 (m, 2H), 3,22-3,18 (m, 1H), 3,14-3,11 (m, 1H), 3,05-2,96 (m, 2H), 2,71-2,68 (m, 1H), 2,42-2,37 (m, 1H), 1,49 (q, *J*= 6,6 Hz, 6H), 1,17 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 403,1).

EJEMPLO 33

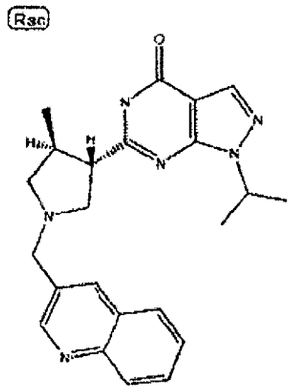
1-isopropil-6-[(3,4-trans)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,84-8,81 (m, 2H), 8,04-8,00 (m, 2H), 7,96 (s, 1H), 7,91-7,88 (m, 1H), 5,09-5,02 (m, 1H), 4,01-3,87 (m, 2H), 3,14-3,93 (m, 4H), 2,72-2,66 (m, 1H), 2,39-2,34 (m, 1H), 1,47 (dd, *J*= 6,6, 1,2 Hz, 6H), 1,15 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 404,1).

EJEMPLO 34

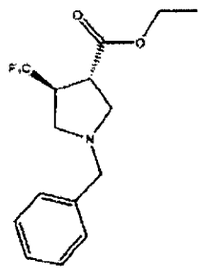
1-isopropil-6-[(3,4-trans)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinolin-3-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,87 (d, *J*= 2,1 Hz, 1H), 8,30 (d, *J*= 1,2 Hz, 1H), 7,99 (d, *J*= 8,7 Hz, 1H), 7,97 (s, 1H), 7,90 (d, *J*= 7,5 Hz, 1H), 7,74-7,69 (m, 1H), 7,60-7,56 (m, 1H), 5,06-4,99 (m, 1H), 3,97-3,87 (m, 2H), 3,13-3,09 (m, 1H), 3,05-3,02 (m, 2H), 2,97-2,93 (m, 1H), 2,73-2,66 (m, 1H), 2,39-2,35 (m, 1H), 1,46 (dd, *J*= 6,6, 2,3 Hz, 6H), 1,15 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 403,1).

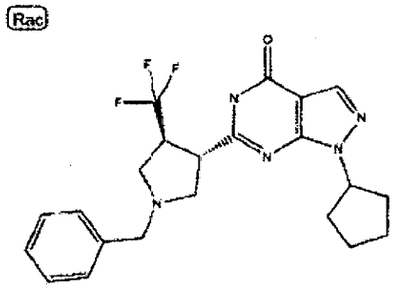
EJEMPLO 35

(a) (3,4-trans)-1-bencil-4-(trifluorometil)pirrolidin-3-carboxilato de etilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo, pero sustituyendo por (E)-4,4,4-trifluorobut-2-enoato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,33-7,22 (m, 5H), 4,16 (q, *J*= 7,1 Hz, 2H), 3,65-3,56 (m, 2H), 3,40-3,32 (m, 1H), 3,12-3,07 (m, 1H), 2,90-2,76 (m, 3H), 2,70-2,66 (m, 1H), 1,24 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 302,1).

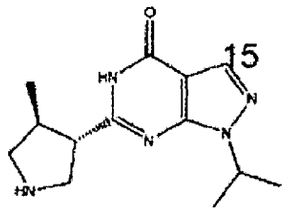
(b) 6-[(3,4-trans)-1-bencil-4-(trifluorometil)pirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-(trifluorometil)pirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,38-7,26 (m, 5H), 5,15-5,11 (m, 1H), 3,83 (d, *J*= 12,5 Hz, 1H), 3,64 (d, *J*= 12,5 Hz, 1H), 3,44-3,41 (m, 1H), 3,34 (t, *J*= 9,1 Hz, 1H), 3,12-3,10 (m, 1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,70-2,65 (m, 1H), 2,55-5,50 (m, 1H), 2,11-1,93 (m, 4H), 1,72-1,66 (m, 2H), 0,86-0,83 (m, 2H). EM: (M^+H m/z = 432,0).

EJEMPLO 36

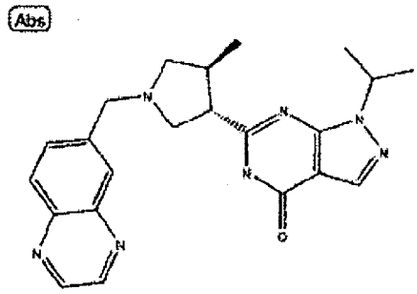
(a) 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H) ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3S,4S)-1-bencil-4-

metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H (CD_3OD) δ 8,02 (s, 1H), 5,11-5,08 (m, 1H), 3,80-3,74 (m, 2H), 3,64-3,57 (m, 1H), 3,30-3,22 (m, 1H), 3,07-3,02 (m, 1H), 2,75-2,71 (m, 1H), 1,49 (dd, *J*= 6,6, 1,7 Hz, 6H), 1,15 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 262,2).

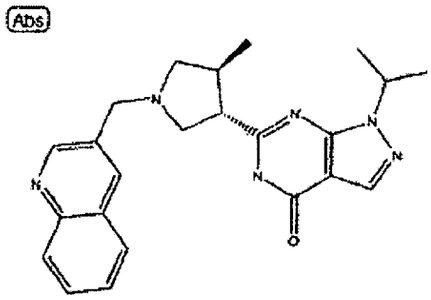
(b) 1-isopropil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 11,0 (sa, 1H), 8,81 (s, 2H), 8,13 (d, *J*= 8,7, 1H), 8,01-7,92 (m, 3H), 5,01-4,94 (m, 1H), 4,01-3,88 (m, 2H), 3,37 (t, *J*= 8,3, 1H), 3,05 (d, *J*= 9,9, 1H), 2,86-2,85 (m, 1H), 2,70-2,68 (m, 1H), 2,49-2,44 (m, 1H), 2,07-2,01 (m, 1H), 1,48 (dd, *J*= 15,3, 6,6 Hz, 6H), 1,20 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z 404,1).

EJEMPLO 37

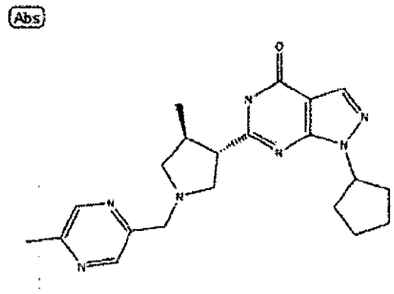
1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinolin-3-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 11,0 (sa, 1H), 8,87 (d, *J*= 2,1 Hz, 1H), 8,29 (s, 1H), 8,07 (d, *J*= 8,3 Hz, 1H), 8,02 (s, 1H), 7,90-7,88 (m, 1H), 7,70-7,66 (m, 1H), 7,56-7,51 (m, 1H), 5,01-4,92 (m, 1H), 4,03-3,83 (m, 2H), 3,40 (t, *J*= 8,7 Hz, 1H), 3,07 (d, *J*= 9,5 Hz, 1H), 2,89-2,86 (m, 1H), 2,68-2,67 (m, 1H), 2,48-2,47 (m, 1H), 2,08-2,02 (m, 1H), 1,48 (dd, *J*= 6,6, 16,59 Hz, 6H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 403,1).

EJEMPLO 38

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

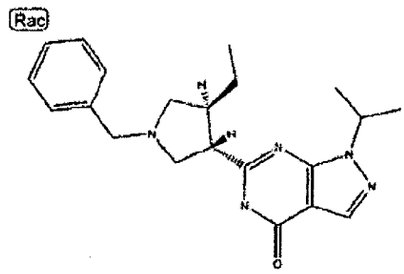


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 5-metilpirazin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,53 (s, 1H), 8,53 (s, 1H), 8,01 (s, 1H), 5,16-5,05 (m, 1H), 4,02 (d, *J*= 14,1 Hz, 1H), 3,74 (d, *J*= 14,1 Hz, 1H), 3,45-3,41 (m, 1H), 3,38 (t, *J*= 8,3 Hz, 1H), 3,08 (d, *J*= 9,9 Hz, 1H), 2,84-2,83 (m, 1H), 2,62-2,54 (m, 1H), 2,52 (s, 3H), 2,47-2,40 (m, 1H), 2,14-1,89 (m, 6H), 1,71-1,64 (m, 2H), 1,24-1,16 (m,3H). EM: (M^+H m/z = 394,1).

EJEMPLO 39

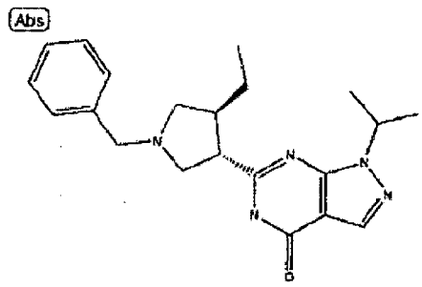
6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-isopropil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-etilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H (CD_3OD) δ 8,01 (s, 1H), 7,38-7,22 (m, 5H), 5,06-5,01 (m, 1H), 3,76-3,64 (m, 2H), 3,12 (t, *J*= 8,71 Hz, 1H), 3,00-2,91 (m, 2H), 2,87-2,82 (m, 1H), 2,51-2,47 (m, 1H), 2,30-2,26 (m, 1H), 1,60-1,50 (m, 2H), 1,49 (d, *J*= 7,05 Hz, 6H), 3,08 (d, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 366,1).

EJEMPLO 40

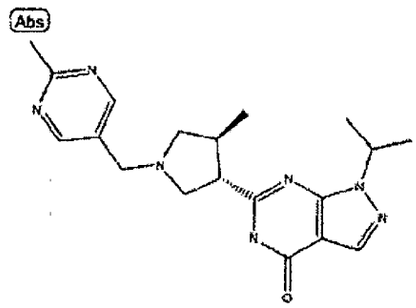
6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El racemato se separó en una columna de HPLC quiral Chiralcel OJ, fase móvil 80/20 heptano/EtOH, t_R = 9,177, para proporcionar el enantiómero. 400 MHz RMN ^{1}H (CD_3OD) δ 8,01 (s, 1H), 7,38-7,22 (m, 5H), 5,06-5,01 (m, 1H), 3,76-3,64 (m, 2H), 3,12 (t, *J*= 8,71 Hz, 1H), 3,00-2,91 (m, 2H), 2,87-2,82 (m, 1H), 2,51-2,47 (m, 1H), 2,30-2,26 (m, 1H), 1,60-1,50 (m, 2H), 1,49 (d, *J*= 7,05 Hz, 6H), 3,08 (d, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 366,2).

EJEMPLO 41

1-isopropil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

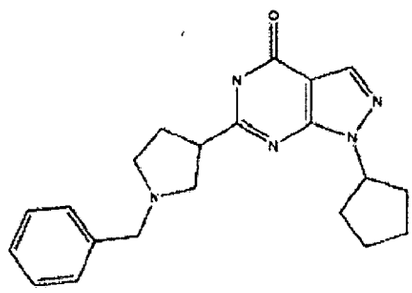


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-

isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 2-metilpirimidina-5-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,68 (s, 2H), 7,97 (s, 1H), 5,08-5,01 (m, 1H), 3,78-3,68 (m, 2H), 3,08-2,92 (m, 4H), 2,74-2,67 (m, 1H), 2,65 (s, 3H), 2,36-2,32 (m, 1H), 1,48 (d, *J*= 6,6 Hz, 6H), 1,15 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 368,1).

EJEMPLO 42

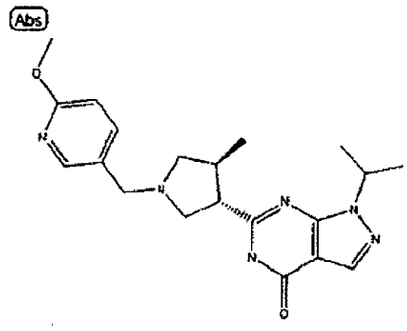
6-(1-bencilpirrolidin-3-il)-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y 1-bencilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (s, 1H), 7,39-7,32 (m, 4H), 7,27-7,23 (m, 1H), 5,12-5,09 (m, 1H), 3,84 (d, *J*= 12,4 Hz, 1H), 3,61 (d, *J*= 12,4 Hz, 1H), 3,30-3,26 (m, 1H), 3,18-3,14 (m, 1H), 3,01 (d, *J*= 9,9 Hz, 1H), 2,45-2,32 (m, 3H), 2,11-1,90 (m, 7H), 1,71-1,65 (m, 2H). EM: (M^+H m/z = 364,1).

EJEMPLO 43

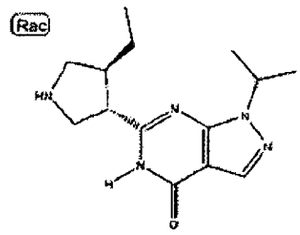
1-isopropil-6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 6-metoxinicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 2H), 7,72 (m, 1H), 6,77 (d, *J*= 8,3 Hz, 1H), 3,90 (s, 3H), 3,73-3,53 (m, 2H), 3,39-3,33 (m, 1H), 3,30 (m, 1H), 2,8 (m, 1H), 2,55-2,40 (m, 1H), 1,9 (m, 1H), 1,57-1,53 (m, 2H), 1,52-1,47 (m, 6H), 1,19 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 383,2).

EJEMPLO 44

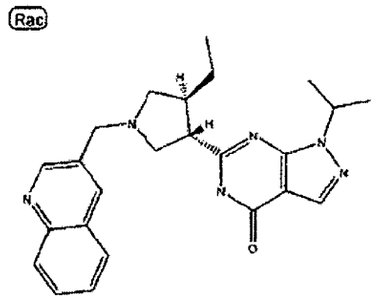
(a) 6-((3,4-trans)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400

MHz RMN ^{1}H (CD_3OD) δ 8,02 (s, 1H), 5,10 (m, 1H), 3,78-3,60 (m, 3H), 3,32-3,28 (m, 1H), 3,10 (m, 1H), 2,62 (m, 1H), 1,65 (m, 1H), 1,58 (m, 1H), 1,49 (dd, *J*= 6,6, 1,7 Hz, 6H), 0,97 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 276,1).

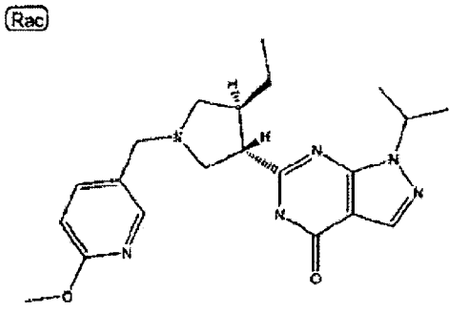
(b) 6-[(3,4-trans)-4-etil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-((3,4-trans)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinolin-3-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,86 (d, *J*= 2,1 Hz, 1H), 8,29 (d, *J*= 1,7 Hz, 1H), 7,98 (d, *J*= 8,3 Hz, 1H), 7,97 (s, 1H), 7,89 (d, *J*= 8,3 Hz, 1H), 7,73-7,68 (m, 1H), 7,59-7,55 (m, 1H), 5,05-4,98 (m, 1H), 3,94-3,85 (m, 2H), 3,13-3,09 (m, 1H), 3,02-2,94 (m, 3H), 2,57-2,52 (m, 1H), 2,39-2,34 (m, 1H), 1,58-1,48 (m, 2H), 1,48 (d, *J*= 6,6 Hz, 6H) 10,87 (t, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 417,0).

EJEMPLO 45

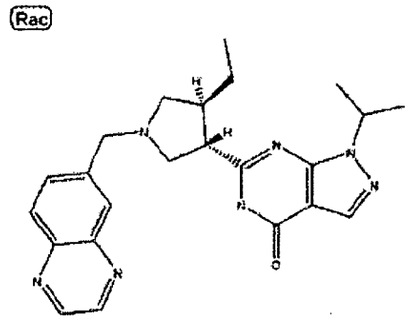
6-{(3,4-trans)-4-etil-1-[(6-metoxipiridin-3-il)metil]pirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-((3,4-trans)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 6-metoxinicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,83 (sa, 1H), 8,02 (d, J= 2,1 Hz, 1H), 8,00 (s, 1H), 7,69 (dd, *J*= 8,7, 2,1 Hz, 1H), 6,77 (d, *J*= 8,3 Hz, 1H), 4,98-4,94 (m, 1H), 3,89 (s, 3H), 3,69-3,54 (m, 2H), 3,29 (t, *J*= 8,5 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,88-2,87 (m, 1H), 2,55 (m, 1H), 2,18 (m, 1H), 1,91 (m, 1H), 1,60-1,55 (m, 1H), 1,51-1,47 (m, 7H), 0,91 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 397,0).

EJEMPLO 46

6-[(3,4-trans)-4-etil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

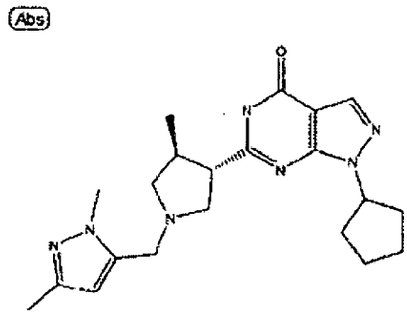


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-((3,4-trans)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,83 (sa, 1H), 8,81 (s, 2H), 7,79 (d, *J*= 2,5 Hz, 1H), 8,15-7,92 (m, 3H), 4,99-4,92 (m, 1H), 3,98-3,86 (m, 2H), 3,35 (t, *J*= 8,7 Hz, 1H), 3,04 (d, *J*= 9,9 Hz, 1H), 2,92-2,91 (m, 1H), 2,61-2,57 (m, 1H), 2,25-2,2 (m, 1H), 2,02 (t, *J*= 8,7 Hz, 1H), 1,64-1,52 (m, 1H), 1,50-1,45 (m, 7H), 0,91 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 418,1).

EJEMPLO 47

1-ciclopentil-6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

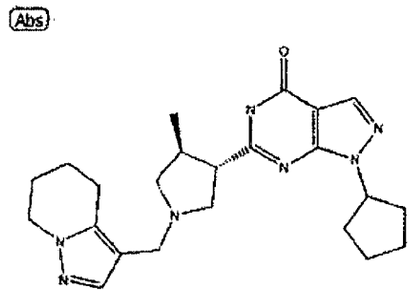


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 1,3-dimetil-1H-pirazol-5-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,99 (s, 1H), 5,95-5,94 (m, 1H), 5,14-5,09 (m, 1H), 3,87 (s, 3H), 3,81 (s, 1H), 3,66 (q, *J*= 14,5 Hz, 2H), 3,33 (t, *J*= 8,3 Hz, 1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,84-2,82 (m, 1H), 2,59-2,55 (m, 1H), 2,44-2,41 (m, 1H), 2,20-2,19 (m, 3H), 2,12-1,90 (m, 5H),

1,70-1,65 (m, 2H), 1,25-1,18 (m, 3H). EM: (M^+H m/z = 396,1).

EJEMPLO 48

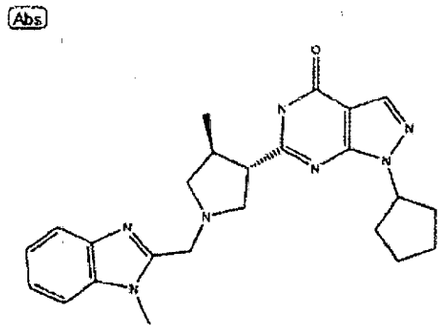
1-ciclopentil-6-[(3S,4S)-4-metil-1-(4,5,6,7-tetrahidropirazolo[1,5-a]piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 4,5,6,7-tetrahidropirazolo[1,5-a]piridina-3-carbaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 7,99 (s, 1H), 7,35 (s, 1H), 5,16-5,09 (m, 1H), 4,11-4,06 (m, 2H), 3,68 (d, *J*= 13,3 Hz, 1H), 3,57 (d, *J*= 13,3 Hz, 1H), 3,32 (t, *J*= 8,7 Hz, 1H), 3,00 (d, *J*= 9,9 Hz, 1H), 2,94-2,80 (m, 2H), 2,78-2,77 (m, 1H), 2,49-2,45 (m, 1H), 2,38-2,33 (m, 1H), 2,11-1,83 (m, 11H), 1,73-1,61 (m, 2H), 1,17 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 422,1).

EJEMPLO 49

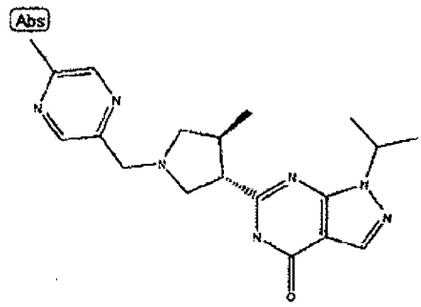
1-ciclopentil-6-{(3S,4S)-4-metil-1-[(1-metil-1H-bencimidazol-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 1-metil-1H-benzo[d]imidazol-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,98 (s, 1H), 7,73 (m, 1H), 7,35 (dd, *J*= 7,1, 1,2 Hz, 1H), 7,29-7,21 (m, 2H), 5,13-5,09 (m, 1H), 4,11-4,06 (m, 2H), 3,97 (s, 3H), 3,37 (t, *J*= 8,3 Hz, 1H), 3,06 (d, *J*= 10,4 Hz, 1H), 2,88-2,85 (m, 1H), 2,77-2,73 (m, 1H), 2,16-1,92 (m, 8H), 1,70-1,66 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 432,1).

EJEMPLO 50

1-isopropil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

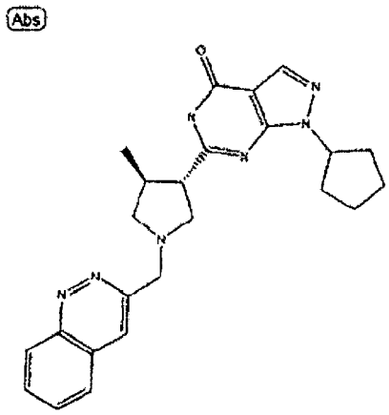


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 5-metilpirazin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 11,4 (sa, 1H), 8,49 (s, 1H), 8,44 (s, 1H), 7,99 (s, 1H), 5,00-4,93 (m, 1H), 4,00-3,97 (m, 1H), 3,78-3,67 (m, 1H), 3,33 (t, *J*= 8,3 Hz, 1H), 3,04 (6, *J*= 9,9 Hz, 1H), 2,85-2,82 (m, 1H), 2,65-2,61 (m, 1H), 2,49 (s, 3H), 2,48-2,41 (m, 1H), 2,13 (t, *J*= 8,5 Hz, 1H), 1,46 (dd, *J*= 11,6 ,6,6 Hz, 6H), 1,17 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z = 368,1).

EJEMPLO 51

6-[(3S,4S)-1-(cinolin-3-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

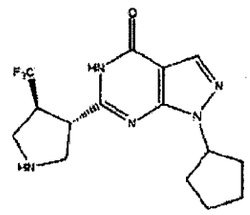


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y cinolin-3-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,49 (d, *J*= 8,7 Hz, 1H), 8,16 (s, 1H), 8,01 (s, 1H), 7,93 (d, *J*= 7,9 Hz, 1H), 7,83-7,81 (m, 1H), 7,79-7,71 (m, 1H), 5,16-5,09 (m, 1H), 4,47-4,44 (m, 1H), 4,35-4,32 (m, 1H), 3,49-3,45 (m,

2H), 3,10-3,07 (m, 1H), 2,87-2,71 (m, 2H), 2,49-2,48 (m, 1H), 2,23 (m, 1H), 2,11-1,87 (m, 5H), 1,73-1,63 (m, 2H), 1,22 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 430,1).

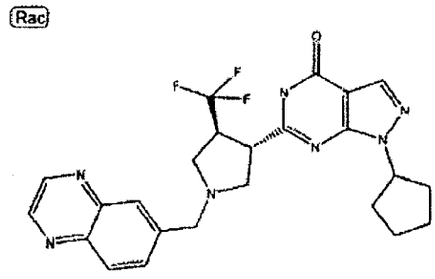
EJEMPLO 52

(a) 1-ciclopentil-6-[(3,4-trans)-4-(trifluorometil)pirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3,4-trans)-1-bencil-4-(trifluorometil)pirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^1H (CD_3OD) δ 7,98 (s, 1H), 5,23 (m, 1H), 3,73 (m, 1H), 3,42 (m, 2H), 3,10 (m, 2H), 2,19-1,92 (m, 7H), 1,75 (m, 2H), 1,23-1,19 (m, 3H).

b) 1-ciclopentil-6-[(3,4-trans)-1-(quinoxalin-6-ilmetil)-4-(trifluorometil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

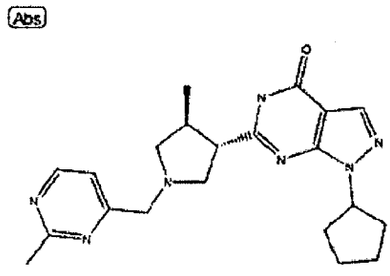


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-

3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3,4-trans)-4-(trifluorometil)pirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,80 (s, 1H), 8,08 (d, *J*= 8,3 Hz, 1H), 7,99 (m, 1H), 7,86-7,83 (m, 1H), 5,13-5,10 (m, 1H), 4,88 (s, 1H), 3,96-3,88 (m, 2H), 3,50-3,35 (m, 2H), 3,17 (t, *J*= 9,9 Hz, 1H), 3,03-2,99 (m, 1H), 2,92-2,88 (m, 1H), 2,79-2,75 (m, 1H), 2,11-1,90 (m, 6H), 1,71-1,65 (m, 1H).

EJEMPLO 53

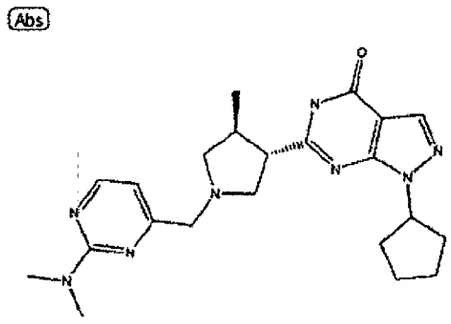
1-ciclopentil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 2-metilpirimidina-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,60 (d, *J*= 5,4 Hz, 1H), 8,03 (s, 1H), 7,24 (s, 1H), 5,18-5,10 (m, 1H), 3,97-3,94 (m, 1H), 3,72-3,68 (m, 1H), 3,40 (t, *J*= 8,3 Hz, 1H), 3,15 (d, *J*= 9,5 Hz, 1H), 2,89 (m, 1H), 2,73 (s, 3H), 2,68-2,63 (m, 1H), 2,53-2,47 (m, 1H), 2,15-1,89 (m, 7H), 1,74-1,65 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 394,1).

EJEMPLO 54

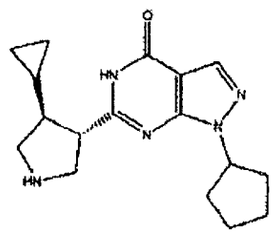
1-ciclopentil-6-[(3S,4S)-1-{[2-(dimetilamino)pirimidin-4-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 2-(dimetilamino)pirimidina-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,24-8,21 (m, 1H), 8,00-7,99 (m, 1H), 6,52-6,50 (m, 1H), 5,13-5,10 (m, 1H), 3,72-3,68 (m, 1H), 3,56-3,52 (m, 1H), 3,46-3,40 (m, 3H), 3,17-3,11 (m,7H), 2,84-2,82 (m, 1H), 2,64-2,60 (m, 1H), 2,44-2,38 (m, 1H), 2,06-1,92 (m, 5H), 1,66-1,65 (m, 2H), 1,20-1,16 (m, 3H). EM: (M^+H m/z = 423,1).

EJEMPLO 55

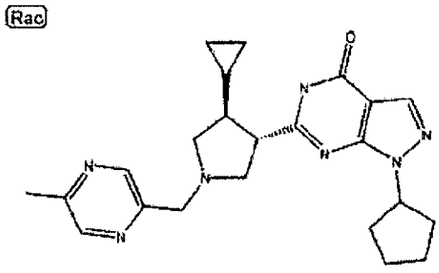
(a) 1-ciclopentil-6-[(3,4-trans)-4-ciclopropilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3,4-trans)-1-bencil-4-ciclopropilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,08-7,94 (m, 1H), 5,17-5,10 (m, 1H), 3,39-3,34 (m, 1H), 3,29-3,28 (m, 2H), 3,17-3,14 (m, 1H), 2,13-1,91 (m, 7H), 1,78-1,67 (m, 3H), 0,82 (m, 1H), 0,47-0,44 (m, 2H), 0,13-0,08 (m, 2H). EM: (M^+H m/z = 314,2).

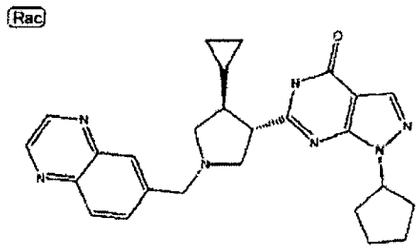
(b) 1-ciclopentil-6-{(3,4-trans)-4-ciclopropil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 1-ciclopentil-6-[(3,4-trans)-4-ciclopropilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 5-metilpirazin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,52 (d, *J*= 0,8 Hz, 1H), 8,46 (s, 1H), 8,00 (s, 1H), 5,14-5,10 (m, 1H), 4,04-4,01 (m, 1H), 3,78-3,75 (m, 1H), 3,35 (t, *J*= 8,7 Hz, 1H), 3,15-3,09 (m, 2H), 2,66-2,64 (m, 1H), 2,52 (s, 3H), 2,38 (t, *J*= 8,7 Hz, 1H), 2,11-2,01 (m, 3H), 1,96-1,91 (m, 2H), 1,73-1,65 (m, 2H), 1,24-1,20 (m, 1H), 0,59-0,83 (m, 2H), 0,53-0,49 (m, 2H), 0,23-0,11 (m, 2H). EM: (M^+H m/z = 420,1).

EJEMPLO 56

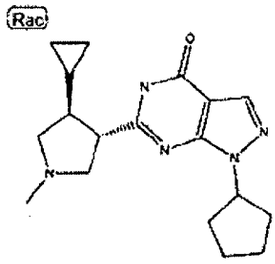
1-ciclopentil-6-[(3,4-trans)-4-ciclopropil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 1-ciclopentil-6-[(3,4-trans)-4-ciclopropilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinoxalin-6-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,82 (s, 2H), 8,14 (d, *J*= 8,7 Hz, 1H), 8,00 (s, 2H), 7,96-7,94 (m, 1H), 5,16-5,09 (m, 1H), 3,98-3,95 (m, 2H), 3,35 (t, *J*= 8,3 Hz, 1H), 3,15-3,08 (m, 2H), 2,70 (m, 1H), 2,27 (m, 1H), 2,15-1,88 (m, 6H), 1,74-1,62 (m, 3H), 0,91-0,87 (m, 1H), 0,55-0,47 (m, 2H), 0,21-0,09 (m, 2H). EM: (M^+H m/z = 456,1).

EJEMPLO 57

1-ciclopentil-6-[(3,4-trans)-4-ciclopropil-1-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

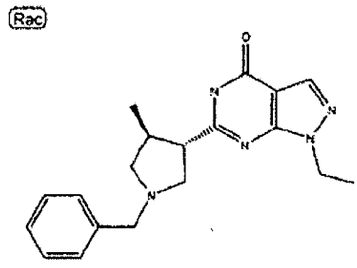


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 1-ciclopentil-6-[(3,4-trans)-4-ciclopropilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y formaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (s, 1H), 5,19-5,11 (m, 1H), 3,31 (d, *J*= 8,7 Hz, 1H), 3,14-3,13 (m, 1H), 3,06 (d, *J*= 9,9 Hz, 1H), 2,57 (m, 1H), 2,43 (s, 3H), 2,14-1,91 (m, 7H), 1,75-1,64 (m, 3H), 0,91-0,82 (m, 1H), 0,53-0,50 (m, 2H), 0,20-0,14 (m, 2H). EM: (M^+H m/z = 328,2).

EJEMPLO 58

6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-etil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

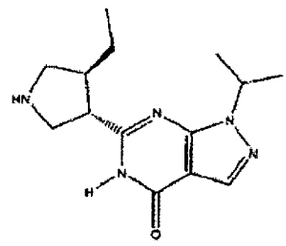


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-etil-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,42-7,27 (m, 5H), 4,38-4,30 (m, 2H), 3,83-3,80 (m, 1H), 3,63-3,59 (m, 1H), 3,49-3,35 (m, 1H), 2,99 (d, *J*= 10,3 Hz, 1H), 2,83-2,80 (m, 1H), 2,55-2,50 (m, 1H), 2,44-2,378 (m, 1H), 1,95-1,90 (m, 1H), 1,47 (t, *J*= 7,1 Hz, 3H), 1,22 (t, *J*= 10,3 Hz, 3H). EM: (M^+H m/z = 338,1).

EJEMPLO 59

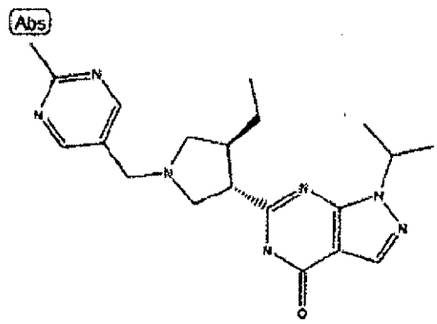
(a) 6-((3S,4S)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-

4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H (CD_3OD) δ 8,02 (s, 1H), 5,10 (m, 1H), 3,78-3,60 (m, 3H), 3,32-3,28 (m, 1H), 3,10 (m, 1H), 2,62 (m, 1H), 1,65 (m, 1H), 1,58 (m, 1H), 1,49 (dd, *J*= 6,6, 1,7 Hz, 6H), 0,97 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 276,1).

(b) 6-{(3,4-trans)-4-etil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

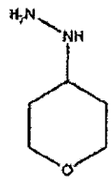


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-((3S,4S)-4-etilpirrolidin-3-il)-1-isopropil-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 2-metilpirimidin-5-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,8 (sa, 1H), 8,62 (s, 2H), 8,01 (s,

1H), 5,00-4,93 (m, 1H), 3,66 (s, 2H), 3,25-3,20 (m, 1H), 3,02 (d, *J*= 9,9 Hz, 1H), 2,95-2,92 (m, 1H), 2,70 (s, 3H), 2,62-2,58 (m, 1H), 2,28-2,23 (m, 1H), 1,98 (t, *J*= 8,7 Hz, 1H), 1,62-1,52 (m, 1H), 1,48 (t, *J*= 6,6 Hz, 6H), 1,46-1,42 (m, 1H), 3,08 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z = 382,2).

EJEMPLO 60

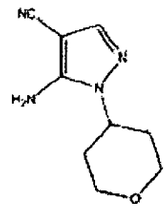
(a) 1-(tetrahidro-2H-piran-4-il)hidrazina



A una disolución de tetrahidropiran-4-ona (71,6 g, 715 mmol) en metanol (2 l) se añadió *terc*-butilcarbazato (100 g, 758 mmol) a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 20 h. La mezcla de reacción se concentró a presión reducida hasta sequedad para dar un sólido blanco (154 g). A una suspensión del sólido blanco (154 g, 715 mmol) en agua (1 l) se añadió ácido acético (500 ml, 8,73 mol) y la mezcla se agitó durante 30 min para obtener una disolución transparente. A esta disolución se añadió poco a poco $NaCNBH_3$ sólido (44,5 g, 708 mmol). La mezcla se agitó a temperatura ambiente durante 2 h. A continuación, la mezcla se transfirió a un matraz de 12 l, se enfrió hasta 0ºC y se inactivó con NaOH 1 N (8,73 l, 8,73 mol). La mezcla se extrajo con CH_2Cl_2 (3 x 3 l) y se secó sobre Na_2SO_4. La fase orgánica se filtró y se concentró para dar un sólido blanco (164 g, contiene ~15% de derivado de N-acetil-N'-Boc-hidrazina). La cromatografía [sílice, acetato de etilo/MeOH (95:5)] dio 94 g de boc-hidrazina pura al 90%. Una disolución de boc-hidrazina (50 g, 231 mmol) en metanol (500 ml) se añadió a una disolución

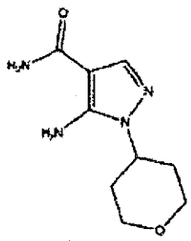
de HCl en dioxano (462 ml, 1,85 mol, 4,0 M). La mezcla se agitó a temperatura ambiente durante la noche. La concentración de la mezcla de reacción a presión reducida dio el compuesto del título como un sólido blanco (43 g, 98%). 400 MHz RMN ^{1}H (DMSO) δ 3,85-3,82 (m, 2H), 3,27-3,21 (m, 2H), 3,13-3,05 (m, 1H), 1,88-1,84 (m, 2H), 1,48-1,38 (m, 2H). EM: (M^+H m/z = 117,2).

(b) 5-amino-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carbonitrilo



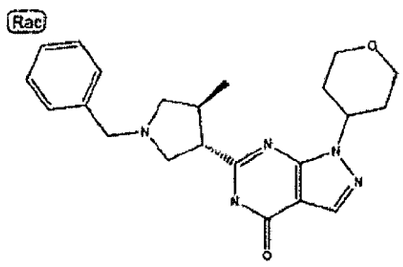
A una mezcla de diclorhidrato de 1-(tetrahidro-2H-piran-4-il)hidrazina (18 g, 96 mmol) en 200 ml de EtOH se añadió Et_3N (30 g, 40 ml, 288 mmol) a 0ºC (baño de hielo). La mezcla resultante se agitó durante 1 h, luego se añadió lentamente una disolución de 2-(etoximetilen)malononitrilo (12 g, 96 mmol) en 100 ml de EtOH para mantener la temperatura de reacción por debajo de 5ºC. Esta mezcla se agitó a temperatura ambiente durante la noche y luego se calentó a reflujo durante 2 h. Después de eliminarse el disolvente a vacío, el residuo se lavó con 300 ml de agua. El sólido se recogió, se lavó con 200 ml de agua adicionales, 200 ml de 1:1 de hexano y éter, se secó para dar 17 g de sólido amarillo. 400 MHz RMN ^{1}H (CD_3OD) δ 7,71 (s, 1H), 4,29-4,21 (m, 1H), 4,02 (dd, *J*= 11,6, 4,6 Hz, 2H), 3,28 (t, *J*= 1,7 Hz, 2H), 2,12-2,02 (m, 2H), 1,80-1,76 (m, 2H). EM: (M^+H m/z = 193,1).

(c) 5-amino-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carboxamida



Una disolución con agitación de 5-amino-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carbonitrilo (~228 mmol) en etanol (300 ml) se trató con H_2O_2 acuosa al 35% (100 ml) seguido por amoniaco acuoso (300 ml). La mezcla de reacción se agitó durante 48 h a temperatura ambiente y luego se inactivó con tiosulfato de sodio saturado ac (800 ml) y se concentró a presión reducida para eliminar la mayoría del etanol. El sólido resultante se eliminó mediante filtración y se lavó con agua (2 x 200 ml) y éter (2 x 150 ml). El sólido se secó a vacío hasta peso constante (31 g, 65% de rendimiento durante 2 etapas). 400 MHz RMN ^{1}H (CD_3OD) δ 7,67 (s, 1H), 4,27-4,21 (m, 1H), 4,03 (dd, *J*= 11,6, 4,6 Hz, 2H), 3,28 (t, *J*= 1,7 Hz, 2H), 2,14-2,04 (m, 2H), 1,81-1,78 (m, 2H). EM: (M^+H m/z = 382,2).

(d) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

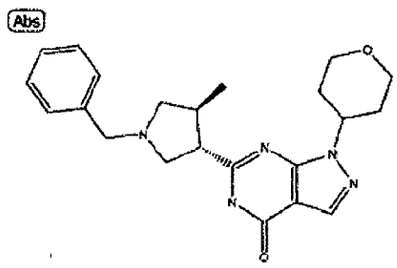


A una mezcla de 5-amino-1-(tetrahidro-2H-piran-4-il-1H-pirazol-4-carboxamida (6,0 g, 28,54 mmol) y (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo (13,3 g, 57,08 mmol) se añadieron tamices moleculares (gránulos). A la mezcla con agitación se añadió una disolución 1,0 M de *t*-BuOK

en THF (57,1 ml, 57,08 mmol) y la mezcla resultante se calentó a reflujo bajo una atmósfera de nitrógeno con agitación vigorosa durante la noche. El análisis de la mezcla de reacción por EM/CL indicó el consumo del material de partida. La mezcla de reacción se enfrió hasta temperatura ambiente y los sólidos se eliminaron mediante filtración. Los sólidos se lavaron con EtOAc (2 x) y los filtrados combinados se concentraron a presión reducida. El resto se repartió entre CH_2Cl_2 y H_2O y las fases acuosas y orgánicas se separaron. La fase acuosa se extrajo con CH_2Cl_2 (1 x) y los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida. El residuo restante se purificó mediante cromatografía (gel de sílice, 1% de Et_3N en EtOAc) para dar el compuesto del título (7,8 g, 70% de rendimiento) como un sólido blanquecino. 400 MHz RMN ^1H ($CDCl_3$) δ 8,02 (s, 1H), 7,39-7,25 (m, 6H), 4,83-4,75 (m, 1H), 4,14-4,09 (m, 2H), 3,82 (m, 1H), 3,62-3,54 (m, 3H), 3,39-3,37 (m, 1H), 3,00 (m, 1H), 2,83 (m, 1H), 2,66-2,27 (m, 4H), 2,10-1,83 (m,3H), 1,20 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 394,2).

EJEMPLO 61

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

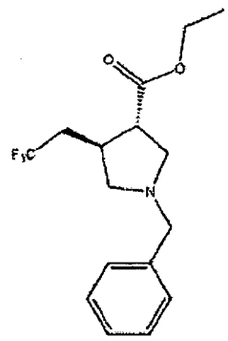


El racemato del ejemplo 60 se separó en una columna de HPLC quiral Chiralcel OD-H, fase móvil 70/30 heptano/EtOH, t_R = 11,465, para proporcionar

el enantiómero. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,39-7,25 (m, 6H), 4,82-4,76 (m, 1H), 4,14-4,09 (m, 2H), 3,82-3,79 (m, 1H), 3,62-3,54 (m, 3H), 3,37 (d, *J*= 8,7 Hz, 1H), 3,00 (d, *J*= 9,9 Hz , 1H), 2,79 (dd, *J*= 6,3, 2,5 Hz , 1H), 2,52-2,48 (m, 1H), 2,42-2,30 (m, 3H), 1,94-1,82 (m, 3H), 1,20 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 394,2).

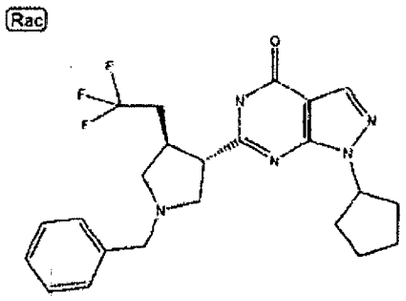
EJEMPLO 62

(a) (3,4-trans)-1-bencil-4-(2,2,2-trifluoroetil)pirrolidin-3-carboxilato de etilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo, pero sustituyendo por (E)-5,5,5-trifluoropent-2-enoato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,32-7,21 (m, 5H), 4,18-4,10 (m, 2H), 3,67-3,55 (m, 2H), 2,90-2,63 (m, 4H), 2,43-2,34 (m, 2H), 2,24-2,15 (m, 1H), 1,27-1,22 (m, 3H), 0,88-0,85 (m, 1H).

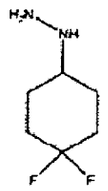
(b) 6-[(3,4-trans)-1-bencil-4-(2,2,2-trifluoroetil)pirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclopentil-1H-pirazol-4-carboxamida y (3,4-trans)-1-bencil-4-(2,2,2-trifluoroetil)pirrolidin-3-carboxilato de etilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,36-7,26 (m, 5H), 5,12-5,08 (m, 1H), 3,85-3,81 (m, 1H), 3,60-3,57 (m, 1H), 3,42 (t, *J*= 8,3 Hz, 1H), 3,02-2,96 (m, 2H), 2,64 (m, 1H), 2,53-2,44 (m, 2H), 2,34-1,89 (m, 6H), 1,81-1,62 (m, 4H).

EJEMPLO 63

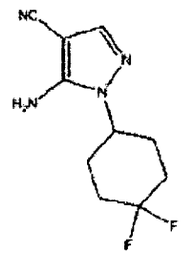
(a) 1-(4,4-difluorociclohexil)hidrazina



A una disolución de 4,4-difluorociclohexanol (0,9 g) en tolueno se añadió trifenilfosfina (2,6 g) y di-*t*-butildiazacarboxalato (1,82 g) y la mezcla de reacción se agitó durante 18 h. La mezcla de reacción se concentró y se añadió metanol (13 ml). A la disolución de metanol se añadió HCl en dioxano (4 M, 13 ml). La mezcla de reacción se agitó durante 3 h y se concentró. La mezcla de reacción se repartió entre agua y acetato de etilo. Las fases se separaron y la fase

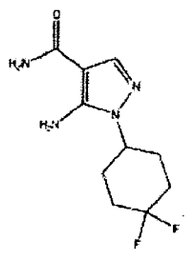
acuosa se extrajo 3x con acetato de etilo. La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró. El compuesto del título se usó sin purificación en la preparación de 5-amino-1-(4,4-difluorociclohexil)-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H (CD_3OD) δ 2,15-2,07 (m, 4H), 2,00-1,81 (m, 2H), 1,68-1,58 (m, 2H). (M^+H m/z = 279,0).

b) 5-amino-1-(4,4-difluorociclohexil)-1H-pirazol-4-carbonitrilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-(4,4-difluorociclohexil)hidrazina. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,5 (m, 1H), 3,90 (m, 1H), 2,40-1,00 (m, 8H).

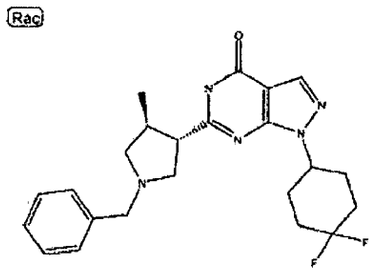
(c) 5-amino-1-(4,4-difluorociclohexil)-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-1-(4,4-difluorociclohexil)-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H (CD_3OD) δ 8,01 (s, 1H), 4,19 (m, 1H), 2,22-1,90 (m, 8H).

(d) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(4,4-difluorociclohexil)-

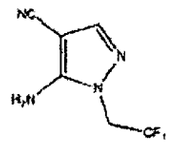
1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-(4,4-difluorociclohexil)-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,40-7,25 (m, 5H), 4,73-4,67 (m, 1H), 3,85-3,82 (m, 1H), 3,64-3,61 (m, 1H), 3,38 (t, *J*= 8,7 Hz, 1H), 3,00 (m, 1H), 2,83 (m, 1H), 2,56-2,52 (m, 1H), 2,43-2,25 (m, 5H), 2,04-1,90 (m, 5H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 428,1).

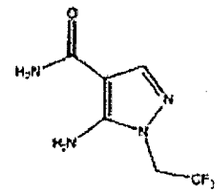
EJEMPLO 64

(a) 5-amino-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carbonitrilo



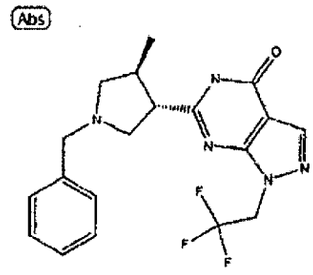
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-(2,2,2-trifluoroetil)hidrazina. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,60 (s, 1H), 4,59 (m, 2H), 4,40 (sa, 2H).

(b) 5-amino-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H (DMSO) δ 7,75 (s, 1H), 7,30 (sa, 1H), 6,78 (sa, 1H) 6,58 (m, 2H), 4,88 (m, 2H).

(c) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2,2,2-trifluoroetil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

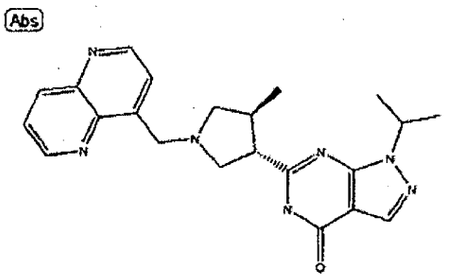


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-(2,2,2-trifluoroetil)-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,15 (s, 1H), 7,59-7,57 (m, 2H), 7,44-7,41 (m, 3H), 4,96-4,88 (m, 2H), 4,22-4,11 (m, 2H), 3,57-3,37 (m, 4H), 2,85 (m, 2H), 1,26-1,23 (m, 3H). EM: (M^+H m/z = 392,1).

EJEMPLO 65

1-isopropil-6-[(3S,4S)-4-metil-1-(1,5-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-

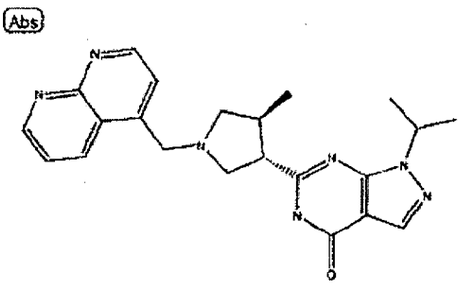
dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 1,5-naftiridin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 9,09-9,08 (m, 1H), 8,95-8,87 (m, 1H), 8,44-8,39 (m, 1H), 8,00 (s, 1H), 7,73-7,70 (m, 1H), 7,67-7,64 (m, 1H), 5,00-4,96 (m, 1H), 4,56-4,53 (m, 1H), 4,33-4,29 (m, 1H), 3,34 (t, *J*= 8,3 Hz , 1H), 3,19 (d, *J*= 9,5 Hz , 1H), 2,91-2,82 (m, 2H), 2,47-2,43 (m, 1H), 2,12 (t, *J*= 8,3 Hz, 1H), 1,48 (dd, *J*= 9,9, 6,6 Hz, 6H), 1,18 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z = 404,2).

EJEMPLO 66

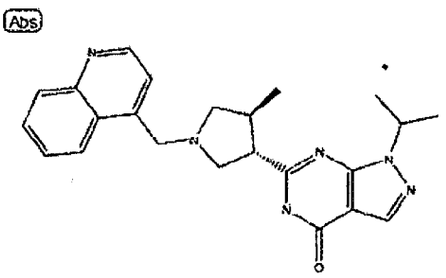
1-isopropil-6-[(3S,4S)-4-metil-1-(1,8-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 1,8-naftiridin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 9,15(dd, *J*= 4,1, 1,7 Hz, 1H), 9,07 (d, *J*= 4,6 Hz, 1H), 8,69 (dd, *J*= 8,3, 1,66 Hz, 1H), 7,99 (s, 1H), 7,69-7,65 (m, 1H), 7,46 (d, *J*= 4,6 Hz, 1H), 5,00-4,93 (m, 1H), 4,14 (s, 3H), 3,26 (t, *J*= 8,3 Hz , 1H), 3,03 (d, *J*= 9,5 Hz , 1H), 2,92-2,90 (m, 1H), 2,80-2,76 (m, 1H), 2,52-2,43 (m, 1H), 1,50-1,46 (m, 6H), 1,20 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 404,1).

EJEMPLO 67

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

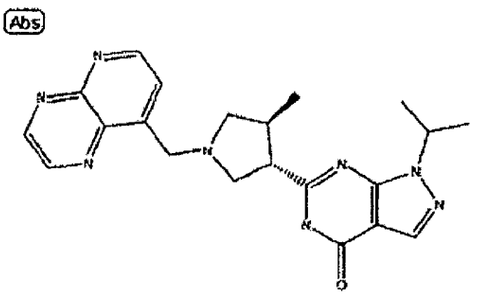


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d}pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y quinolin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,63 (sa, 1H), 8,85 (d, *J*= 4,6 Hz, 1H), 8,26-8,24 (m, 1H), 8,13-8,11 (m, 1H), 7,99 (s, 1H), 7,77-7,69 (m, 2H), 7,39 (d, *J*= 4,6 Hz, 1H), 5,00-4,94 (m, 1H), 4,13 (d, *J*= 3,3 Hz, 2H), 3,32 (t,

J= 8,3 Hz, 1H), 3,06 (d, *J*= 9,5 Hz, 1H), 2,89-2,87 (m, 1H), 2,74-2,70 (m, 1H), 2,46-2,42 (m, 1H), 2,04 (t, *J*= 8,7 Hz, 1H), 1,48 (dd, *J*= 12,9, 7,1 Hz, 6H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 403,2).

EJEMPLO 68

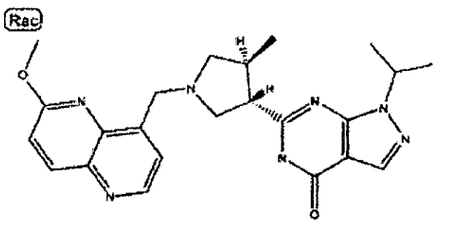
1-isopropil-6-[(3S,4S)-4-metil-1-(pirido[2,3-b]pirazin-8-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y pirido[2,3-b]pirazin-8-carbaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 10,00 (sa, 1H), 9,16-9,10 (m, 3H), 8,00 (s, 1H), 7,78 (m, 1H), 5,00-4,97 (m, 1H), 4,63-4,58 (m, 1H), 4,34-4,18 (m, 1H), 3,30 (m, 1H), 3,27 (m, 1H), 2,92-2,77 (m, 2H), 2,49-2,38 (m, 1H), 2,09-1,97 (m, 1H), 1,48 (dd, *J*= 10,8, 6,6 Hz, 6H), 1,20 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 405,2).

EJEMPLO 69

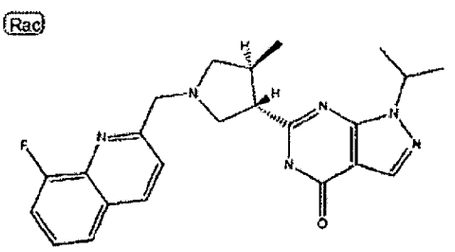
1-isopropil-6-{(3,4-trans)-1-[(6-metoxi-1,5-naftiridin-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 6-metoxi-1,5-naftiridin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,78 (d, *J*= 4,6 Hz, 1H), 8,21 (d, *J*= 9,1 Hz, 1H), 8,01 (s, 1H), 7,63 (m, 1H), 7,17 (d, *J*= 9,1 Hz, 1H), 5,01-4,95 (m, 1H), 4,4 (m, 1H), 4,07 (s, 3H), 3,48 (m, 1H), 3,18 (m, 1H), 2,89-2,75 (m, 2H), 2,43 (m, 1H), 2,10-2,08 (m, 2H), 1,49 (dd, *J*= 11,6, 6,6 Hz, 6H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 434,2).

EJEMPLO 70

6-{(3,4-trans)-1-[(8-fluoroquinolin-2-il)metil]-4-metilpirrolidin-3-il}-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

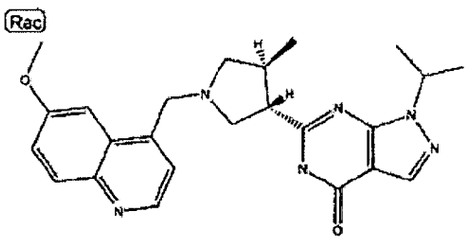


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-

ona y 8-fluoroquinolin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,27-8,25 (m, 1H), 8,04 (s, 1H), 7,86 (m, 1H), 7,66-7,60 (m, 1H), 7,50-7,38 (m, 2H), 5,04-4,97 (m, 1H), 4,30 (m, 1H), 4,18 (m, 1H), 3,47 (m, 2H), 3,28 (m, 1H), 3,00 (m, 1H), 2,59 (m, 1H), 2,40 (m, 1H), 1,50 (dd, *J*= 11,2, 6,6 Hz, 6H), 1,22 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 421,2).

EJEMPLO 71

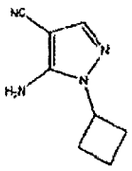
1-isopropil-6-{(v)-1-[(6-metoxiquinolin-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 1-ciclopentil-6-[(3,4-trans)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-isopropil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 6-metoxiquinolin-4-carbaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,87 (d, *J*= 5,0 Hz, 1H), 8,08 (d, *J*= 9,5 Hz, 1H), 8,00-7,95 (m, 2H), 7,70 (d, *J*= 2,5 Hz, 1H), 7,61 (d, *J*= 2,9 Hz, 1H), 5,03-4,97 (m, 1H), 4,08 (s, 3H), 4,08-4,02 (m, 3H), 3,91-3,86 (m, 2H), 3,46-3,41 (m, 1H), 3,33 (s, 1H), 2,94 (m, 1H), 1,48 (d, *J*= 7,1 Hz, 3H), 1,42 (d, *J*= 6,6 Hz, 3H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 433,2).

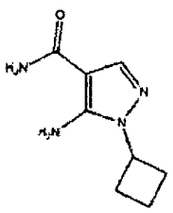
EJEMPLO 72

(a) 5-amino-1-ciclobutil-1H-pirazol-4-carbonitrilo



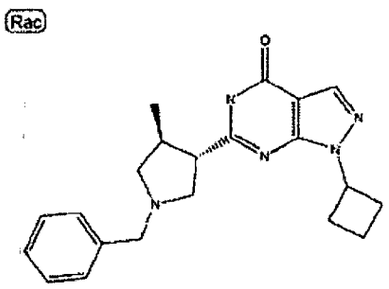
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-ciclobutilhidrazina. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,50 (s, 1H), 4,48-4,40 (m, 1H), 4,23 (m, 2H), 2,70-2,58 (m, 2H), 2,48-2,35 (m, 2H), 1,97-1,79 (m, 2H). EM: (M^+H m/z 163,1).

(b) 5-amino-1-ciclobutil-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-1-ciclobutil-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H (CD_3OD) δ 7,71 (s, 1H), 4,71-4,55 (m, 1H), 2,61-2,50 (m, 2H), 2,46-2,31 (m, 2H), 1,89-1,83 (m, 2H).

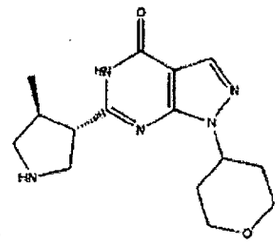
(c) 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-ciclobutil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-ciclobutil-1H-pirazol-4-carboxamida. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,03 (d, *J*= 3,32 Hz, 1H), 7,35-7,24 (m, 5H), 5,25-5,20 (m, 1H), 3,79-3,57 (m, 3H), 3,36-3,32 (m, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,80-2,60 (m, 3H), 2,53-2,38 (m, 3H), 1,92-1,79 (m, 3H), 1,25-1,12 (m, 3H). EM: (M^+H m/z 464,2).

EJEMPLO 73

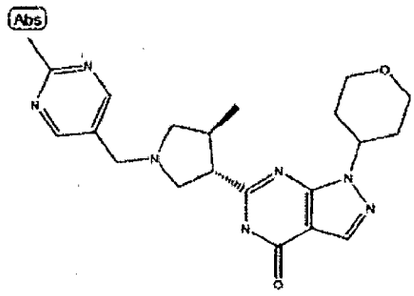
(a) 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



Se disolvió 6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona (5,6 g) en 100 ml de metanol y se añadió a una botella de Parr. Se añadió hidróxido de paladio (3,76 g) junto con 3,56 ml de ácido clorhídrico concentrado. La mezcla de reacción se colocó en un hidrogenador a 40 psi (276 KPa) de H_2 durante 18 h. La mezcla de reacción se filtró a través de Celite y se concentró para proporcionar 4,47 g del compuesto del título como la sal de cloruro de hidrógeno. 400 MHz RMN ^{1}H (CD_3OD) δ 8,03 (s, 1H), 4,49 (m, 1H), 4,09-4,06 (m, 2H), 3,74-3,57 (m, 4H), 3,24 (m, 1H), 3,05 (m, 1H), 2,89 (m, 1H), 2,77 (m, 1H), 2,30 (m, 2H), 1,90 (m, 2H), 1,22 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 304,2).

(b) 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-

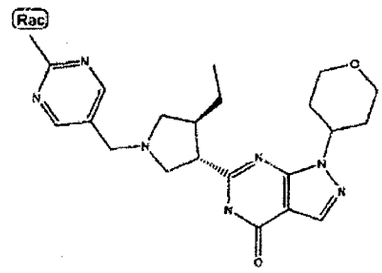
(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de clorhidrato de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (493 mg) en 1,2-dicloroetano (10 ml) se añadió ácido acético (174 mg), 2-metilpirimidin-5-carbaldehído (236 mg) y triacetoxiborohidruro de sodio (635 mg). La mezcla de reacción se calentó a 50°C durante la noche. La mezcla de reacción se concentró sobre gel de sílice y se purificó mediante cromatografía CombiFlash para proporcionar el compuesto del título (146 mg). 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,63 (s, 2H), 8,01 (s, 1H), 4,82-4,76 (m, 1H), 4,12-4,08 (m, 2H), 3,68 (d, *J*= 5,0 Hz, 3H), 3,64-3,54 (m, 2H), 3,28 (t, *J*= 8,3 Hz, 1H), 3,04 (d, *J*= 9,9 Hz, 1H), 2,89-2,86 (m, 1H), 2,71 (s, 3H), 2,66-2,62 (m, 1H), 2,49-2,27 (m, 3H), 1,97 (t, *J*= 7,9 Hz, 1H), 1,91-1,83 (m, 2H), 1,19 (d, *J*= 7,05 Hz, 3H). EM: (M^+H m/z 410,2).

EJEMPLO 74

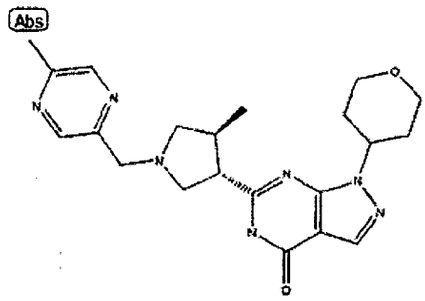
6-{(3,4-trans)-4-etil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por clorhidrato de 6-[(3,4-trans)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,55 (sa, 1H), 8,64 (s, 2H), 8,01 (s, 1H), 4,81-4,73 (m, 1H), 4,11-4,09 (m, 2H), 3,68 (s, 2H), 3,61-3,53 (m, 2H), 3,28 (t, *J*= 8,7 Hz, 1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,94-2,92 (m, 1H), 2,71 (s, 3H), 2,57-2,53 (m, 1H), 2,40-2,20 (m, 3H), 1,96 (t, *J*= 8,7 Hz, 1H), 1,89-1,84 (m, 2H), 1,64-1,57 (m, 1H), 1,52-1,44 (m, 1H), 0,91 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 424,3).

EJEMPLO 75

6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



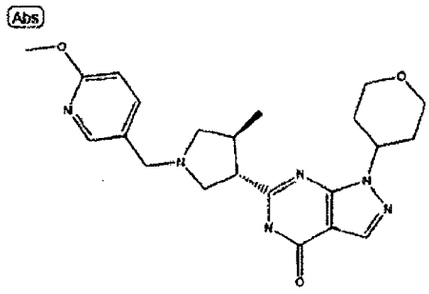
El compuesto del título se proporcionó siguiendo el procedimiento para

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la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-metilpirazin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,53 (s, 1H), 8,47 (s, 1H), 8,03 (s, 1H), 4,83-4,79 (m, 1H), 4,12-4,03 (m, 2H), 3,78-3,75 (m, 1H), 3,61-3,55 (m, 2H), 3,46-3,40 (m, 1H), 3,12-3,09 (m, 1H), 2,87 (m, 1H), 2,64 (m, 1H), 2,53 (m, 2H), 2,47-2,28 (m, 4H), 2,16 (m, 2H), 1,91-1,84 (m, 2H), 1,23-1,20 (m, 3H). EM: (M^+H m/z 410,3).

EJEMPLO 76

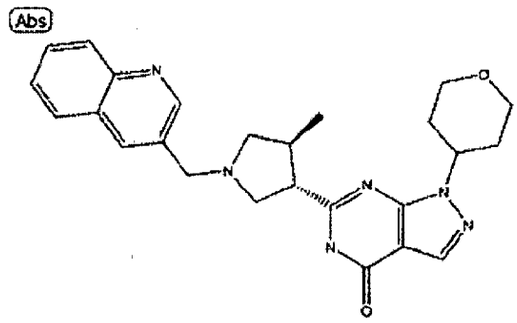
6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-metoxinicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,03 (d, *J*= 2,1 Hz, 1H), 8,01 (s, 1H), 7,69 (dd, *J*= 8,7, 2,5 Hz, 1H), 7,77 (d, *J*= 8,7 Hz, 1H), 4,83-4,75 (m, 1H), 4,14-4,08 (m, 2H), 3,89 (s, 3H), 3,72-3,68 (m, 1H), 3,62-3,3,54 (m, 3H), 3,33 (t, *J*= 8,3 Hz, 1H), 2,99 (d, *J*= 9,9 Hz, 1H), 2,84-2,82 (m, 1H), 2,57-2,53 (m, 1H), 2,43-2,27 (m, 3H), 1,95-1,82 (m,3H), 1,19 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 425,3).

EJEMPLO 77

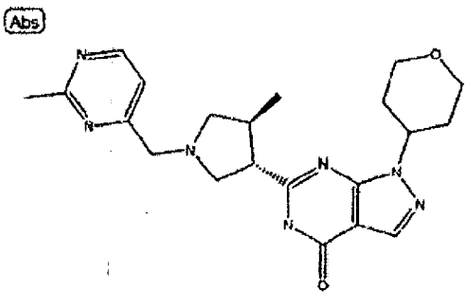
6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-3-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,86 (d, *J*= 2,1 Hz, 1H), 8,27 (d, *J*= 1,7 Hz, 1H), 8,08-8,06 (m, 1H), 8,03 (s, 1H), 7,90-7,57 (m, 1H), 7,70-7,66 (m, 1H), 7,56-7,52 (m, 1H), 4,83-4,75 (m, 1H), 4,11-4,07 (m, 2H), 4,02-3,99 (m, 1H), 3,85-3,82 (m, 1H), 3,60-3,53 (m, 2H), 3,33 (t, *J*= 8,3 Hz, 1H), 3,05 (d, *J*= 9,9 Hz, 1H), 2,87-2,85 (m, 1H), 2,68-2,60 (m, 1H), 2,53-2,40 (m, 1H), 2,38-2,29 (m, 2H), 2,05 (m, 1H), 1,90-1,84 (m, 2H), 1,19 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 445,1).

EJEMPLO 78

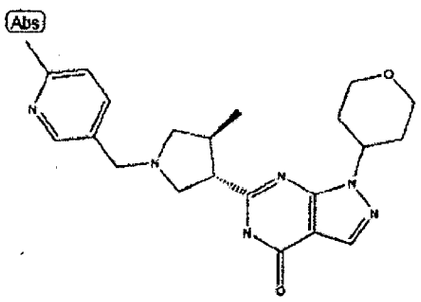
6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 2-metilpirimidin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,59 (d, *J*= 5,0 Hz, 1H), 8,03 (s, 1H), 7,20 (d, *J*= 5,0 Hz, 1H), 4,84-4,76 (m, 1H), 4,13-4,08 (m, 2H), 3,97-3,93 (m, 1H), 3,70-3,67 (m, 1H), 3,61-3,53 (m, 2H), 3,40 (t, *J*= 8,3 Hz, 1H), 3,14 (d, *J*= 9,5 Hz, 1H), 2,88 (m, 1H), 2,72 (s, 3H), 2,69-2,63 (m, 1H), 2,47-2,27 (m, 3H), 2,10-2,08 (m, 1H), 1,91-1,83 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 410,2).

EJEMPLO 79

6-{(3S,4S)-4-metil-1-[(6-metilpiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

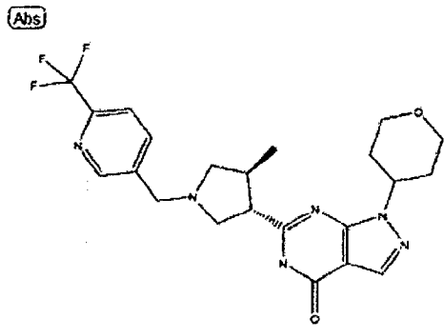


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-

1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-metilnicotinaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 8,38 (d, *J*= 2,1 Hz, 1H), 7,99 (s, 1H), 7,77 (d, *J*= 2,07 Hz, 1H), 7,75 (d, *J*= 2,07 Hz, 1H), 4,94-4,83 (m, 1H), 4,09-4,05 (m, 2H), 3,78-3,57 (m, 4H), 3,31-3,28 (m, 1H), 3,11-3,06 (m, 1H), 3,01-2,91 (m, 2H), 2,72-2,65 (m, 1H), 2,50 (s, 3H), 2,33-2,23 (m, 3H), 1,90-1,86 (m, 2H), 1,14 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 409,2).

EJEMPLO 80

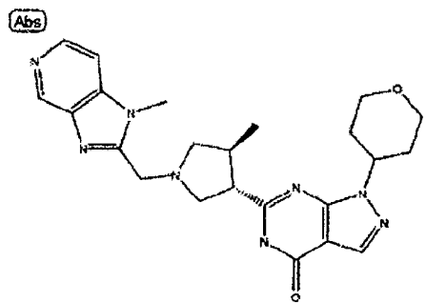
6-[(3S,4S)-4-metil-1-{[6-(trifluorometil)piridin-3-il]metil}pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 6-(trifluorometil)nicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,64 (d, *J*= 1,7 Hz, 1H), 8,01 (s, 1H), 7,99 (d, *J*= 1,7 Hz, 1H), 7,70 (d, *J*= 8,3 Hz, 1H), 4,83-4,77 (m, 1H), 4,13-4,08 (m, 2H), 3,86-3,74 (m, 2H), 3,61-3,53 (m, 2H), 3,30 (t, *J*= 8,7 Hz, 1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,92-2,89 (m, 1H), 2,72-2,67 (m, 1H), 2,50-2,47 (m, 1H), 2,38-2,30 (m, 2H), 2,07-2,03 (m, 1H), 1,91-1,82 (m, 2H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 412,2).

EJEMPLO 81

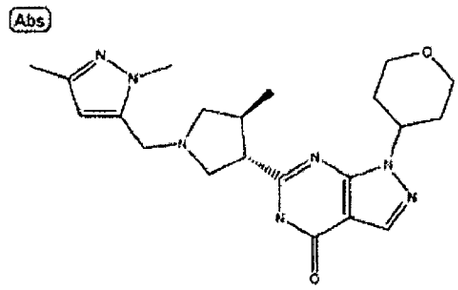
6-{(3S,4S)-4-metil-1-[(1-metil-1H-imidazo[4,5-c]piridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-metil-1H-imidazo[4,5-c]piridin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,83 (sa, 1H), 9,01 (s, 1H), 8,41 (d, *J*= 15,8 Hz, 1H), 7,98 (s, 1H), 7,30 (d, *J*= 4,98 Hz, 1H), 4,79-4,75 (m, 1H), 4,13-4,06 (m, 3H), 4,00-3,96 (s, 4H), 3,60-3,52 (m, 2H), 3,30 (t, *J*= 8,7 Hz, 1H), 3,07 (d, *J*= 9,9 Hz, 1H), 2,92-2,89 (m, 1H), 2,82-2,77 (m, 1H), 2,48-2,45 (m, 1H), 2,36-2,27 (m, 2H), 2,19-2,17 (m, 1H), 1,89-1,79 (m, 2H), 1,23 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 449,2).

EJEMPLO 82

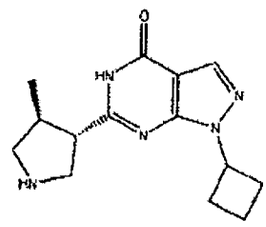
6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1,3-dimetil-1H-pirazol-5-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,98 (s, 1H), 5,94 (s, 1H), 4,81-4,75 (m, 1H), 4,57 (s, 1H), 4,11-4,06 (m, 2H), 3,84 (s, 2H), 3,77 (s, 1H), 3,71-3,52 (m, 2H), 3,31 (t, *J*= 8,3 Hz, 1H), 3,01 (d, *J*= 9,9 Hz, 1H), 2,85-2,83 (m, 1H), 2,62-2,57 (m, 1H), 2,46-2,25 (m, 2H), 2,17-2,16 (m, 6H), 1,96-1,81 (m, 2H), 1,18 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 412,2).

EJEMPLO 83

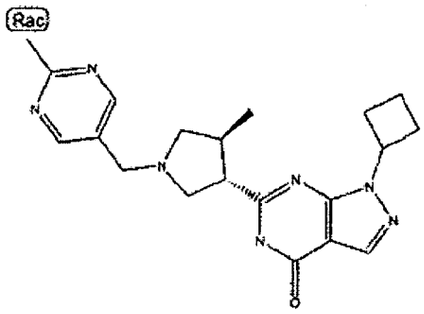
(a) 1-ciclobutil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3,4-trans)-1-

bencil-4-metilpirrolidin-3-il]-1-ciclobutil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H (CD_3OD) δ 8,03 (s, 1H), 5,39 (m, 1H), 3,79-3,38 (m, 4H), 3,08-2,71 (m, 4H), 2,43 (m, 2H), 1,92 (m, 2H), 1,22 (m, 3H). EM: (M^+H m/z 464,2).

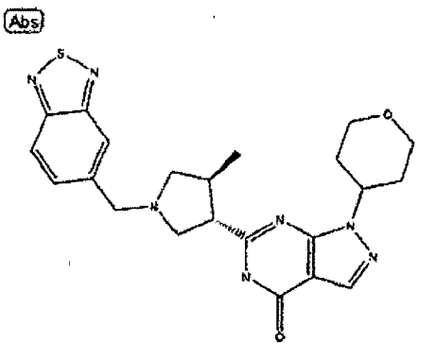
(b) 1-ciclobutil-6-{(3,4-trans)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 1-ciclobutil-6-[(3,4-trans)-4-metilpirrolidin-3-il]-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,79 (sa, 1H), 8,63 (s, 2H), 8,04 (s, 1H), 5,28-5,22 (m, 1H), 3,68 (s, 2H), 3,24 (t, *J*= 8,3 Hz, 1H), 3,04 (d, *J*= 9,9 Hz, 1H), 2,89-2,87 (m, 1H), 2,80-2,67 (m, 5H), 2,51-2,38 (m, 3H), 2,03-1,81 (m, 4H), 1,18 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 480,2).

EJEMPLO 84

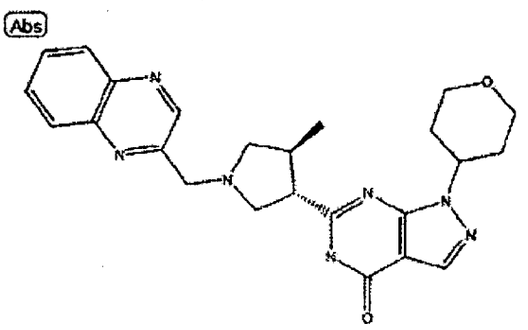
6-[(3S,4S)-1-(2,1,3-benzotiadiazol-5-ilmetil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por benzo[c][1,2,5]tiadiazol-5-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,97 (sa, 1H), 8,02-8,00 (m, 2H), 7,86 (s, 1H), 7,77 (d, *J*= 1,2 Hz, 1H), 4,81-4,75 (m, 1H), 4,12-4,06 (m, 2H), 3,96-3,92 (m, 1H), 3,81-3,78 (m, 1H), 3,60-3,52 (m, 2H), 3,38 (t, *J*= 8,3 Hz, 1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,88-2,85 (m, 1H), 2,68-2,63 (m, 1H), 2,47-2,45 (m, 1H), 2,37-2,28 (m, 2H), 2,04 (t, *J*= 8,7 Hz, 1H), 1,90-1,80 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 452,1).

EJEMPLO 85

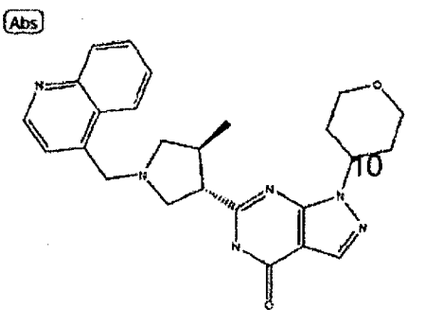
6-[(3S,4S)-4-metil-1-(quinoxalin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinoxalin-2-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 11,57 (sa, 1H), 8,89 (s, 1H), 8,26 (dd, *J*= 8,3, 1,2 Hz, 1H), 8,08-8,05 (m, 2H), 7,78-7,70 (m, 2H), 4,82 (m, 1H), 4,32-4,28 (m, 1H), 4,13-4,08 (m, 2H), 4,00-3,96 (m, 1H), 3,63-3,55 (m, 2H), 3,44 (t, *J*= 8,3 Hz, 1H), 3,26 (d, *J*= 9,9 Hz, 1H), 2,93-2,91 (m, 1H), 2,70-2,69 (m, 1H), 2,39-2,31 (m, 2H), 2,25-2,23 (m, 1H), 2,04 (s, 1H), 1,92-1,84 (m, 2H), 1,23 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 446,2).

EJEMPLO 86

6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

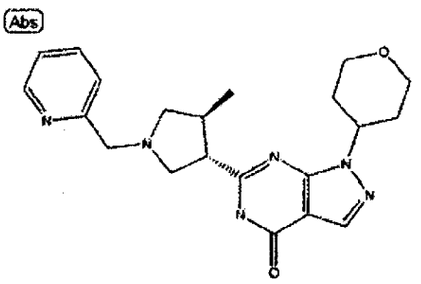


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por quinolin-4-carbaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,68 (sa, 1H), 8,83 (d, *J*= 4,1 Hz, 1H), 8,25-8,22 (m, 1H), 8,12-8,08 (m, 1H), 7,98 (s, 1H), 7,75-7,72 (m, 1H), 7,54 (d, *J*= 3,3 Hz, 1H), 7,36 (d, *J*= 3,3 Hz, 1H), 5,21 (m, 1H), 4,77 (m, 1H), 4,13-4,06 (m, 3H), 3,59-3,52 (m, 2H), 3,32 (d, *J*= 8,7 Hz,

1H), 3,03 (d, *J*= 9,9 Hz, 1H), 2,88-2,86 (m, 1H), 2,72-2,69 (m, 1H), 2,36-2,28 (m, 3H), 2,04-2,00 (m, 1H), 1,89-1,84 (m, 2H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 445,1).

EJEMPLO 87

6-[(3S,4S)-4-metil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

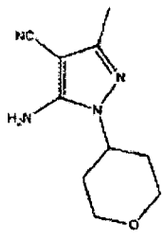


A una disolución de clorhidrato de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (3,98 g) en dimetilformamida (60 ml) se añadió 2-piridilcarbaldehído (1,63 g) seguido por ácido acético (1,34 ml) y triacetoxiborohidruro de sodio (4,99 g). La mezcla de reacción se agitó durante 20 minutos a temperatura ambiente y se inactivó con 24 ml de disolución de NaOH 1 N. La mezcla de reacción se ajustó hasta pH 9 con disolución saturada de bicarbonato sódico, se extrajo 3x con acetato de etilo y se secó con sulfato de magnesio, se filtró y se concentró para dar 3,6 g del compuesto del título. La base libre se disolvió en acetato de etilo y se añadieron 25 ml de HCl/acetato de etilo y se agitó. El sólido blanco se filtró y secó para proporcionar 5,10 g del compuesto del título como una sal de diclorhidrato. 400 MHz RMN ^1H ($CDCl_3$) δ 8,64-8,63 (m, 1H), 8,03 (s, 1H), 7,72-7,67 (m, 1H), 7,43 (d, *J*= 7,9 Hz, 1H), 7,21-7,18 (m, 1H), 4,85-4,75 (m, 1H), 4,14-4,05 (m, 3H), 3,80-3,76 (m, 1H), 3,63-3,54 (m, 2H), 3,47-3,42 (m, 1H),

3,10 (m, 1H), 2,87 (m, 1H), 2,66 (m, 1H), 2,46-2,28 (m, 3H), 2,14 (m, 1H), 1,93-1,84 (m, 2H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 495,2).

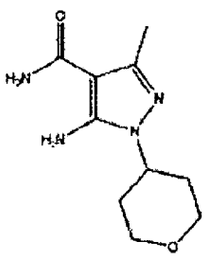
EJEMPLO 88

(a) 5-amino-3-metil-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carbonitrilo



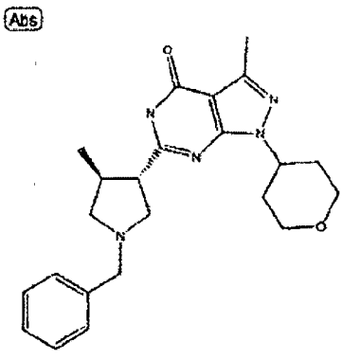
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo, pero sustituyendo por 1-(tetrahidro-2H-piran-4-il)hidrazina y 2-(1-metoxietiliden)malononitrilo. 400 MHz RMN ^1H (CD_3OD) δ 4,20 (m, 1H), 4,05 (m, 2H), 3,50 (m, 2H), 2,18 (s, 3H), 2,09 (m, 2H), 1,77 (m, 2H). EM: (M^+H m/z 207,0).

(b) 5-amino-3-metil-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4 carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-3-metil-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^1H (CD_3OD) δ 4,20 (m, 1H), 4,05 (m, 2H), 3,50 (m, 2H), 2,18 (s, 3H), 2,09 (m, 2H), 1,77 (m, 2H). EM: (M^+H m/z 225,0).

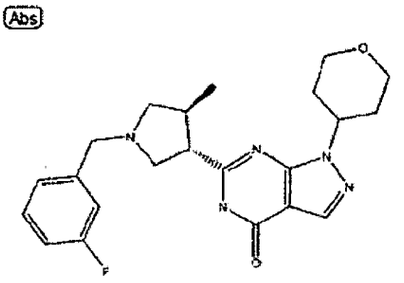
(c) 6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-3-metil-1-(tetrahidro-2H-piran-4-il)-1H-pirazol-4-carboxamida y (3S,4S)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,51-7,30 (m, 5H), 4,75-4,68 (m, 1H), 4,13-4,08 (m, 2H), 3,84-3,73 (m, 1H), 3,63-3,48 (m, 2H), 3,40 (m, 1H), 3,10-2,78 (m, 2H), 2,55 (s, 3H), 2,50-2,24 (m, 3H), 1,87-1,80 (m, 2H), ,61-1,41 (m, 3H), 1,19 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z = 408,1).

EJEMPLO 89

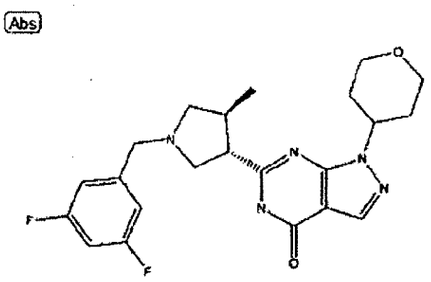
6-[(3S,4S)-1-(3-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 3-fluorobenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,35-7,30 (m, 1H), 7,21-7,20 (m, 1H), 7,05 (d, *J*= 9,5 Hz, 1H), 6,98-6,93 (m, 1H), 4,83-4,77 (m, 1H), 4,14-4,08 (m, 2H), 3,80-3,77 (m, 1H), 3,64-3,54 (m, 3H), 3,36 (t, *J*= 8,8 Hz, 1H), 3,01 (d, *J*= 9,9 Hz, 1H), 2,84-2,83 (m, 1H), 2,57 (m, 1H), 2,44-2,27 (m, 3H), 1,95-1,83 (m, 3H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 412,4).

EJEMPLO 90

6-[(3S,4S)-1-(3,5-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

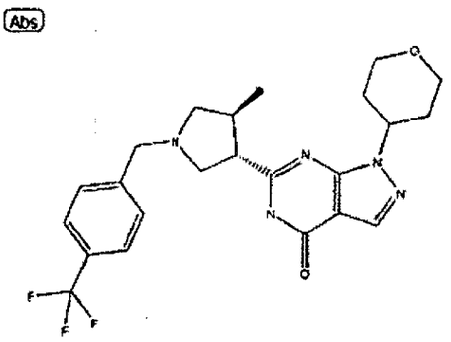


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 3,5-difluorobenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,03 (s, 1H), 6,93-6,90 (m, 2H), 6,73-6,69 (m, 1H), 4,81-4,80 (m, 1H), 4,14-4,10 (m, 2H), 3,79-3,67 (m, 2H), 3,62-3,55 (m, 2H), 3,30-3,26 (m, 1H), 3,10-3,07 (m, 1H), 2,95-2,92 (m, 1H), 2,83-2,79 (m, 1H), 2,26-2,53 (m, 1H), 2,38-2,32 (m, 2H), 2,18-2,14 (m, 1H), 1,91-1,85 (m, 2H),

1,18 (6, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 430,4).

EJEMPLO 91

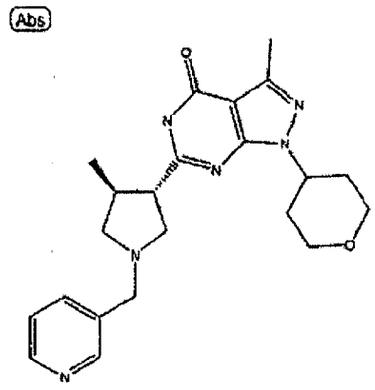
6-{(3S,4S)-4-metil-1-[4-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 4-(trifluorometil)benzaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 8,03 (s, 1H), 7,62-7,59 (m, 2H), 7,51-7,49 (m, 2H), 4,83-4,76 (m, 1H), 4,14-4,08 (m, 2H), 3,87-3,84 (m, 1H), 3,70-3,67 (m, 1H), 3,61-3,54 (m, 2H), 3,34 (t, *J*= 8,3 Hz, 1H), 3,01 (d, *J*= 9,9 Hz, 1H), 2,88-2,86 (m, 1H), 2,67-2,62 (m, 1H), 2,48-2,46 (m, 1H), 2,38-2,30 (m, 2H), 2,05-2,00 (m, 1H), 1,81-1,82 (m, 2H), 1,19 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 462,4).

EJEMPLO 92

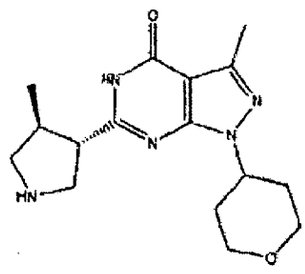
3-metil-6-[(3S,4S)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 3-metil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y nicotinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,53 (m, 2H), 7,83 (d, *J*= 7,9 Hz, 1H), 7,36-7,33 (m, 1H), 4,74-4,68 (m, 1H), 4,12-4,07 (m, 2H), 3,79-3,76 (m, 1H), 3,68-3,65 (m, 1H), 3,59-3,52 (m, 2H), 3,47 (s, 1H), 3,34 (t, *J*= 8,7 Hz, 1H), 2,99 (d, *J*= 9,9 Hz, 1H), 2,82-2,80 (m, 1H), 2,61-2,57 (m, 1H), 2,54 (s, 3H), 2,42-2,28 (m, 2H), 1,95 (t, *J*= 8,7 Hz, 1H), 1,87-1,78 (m, 2H), 1,19 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 409,2).

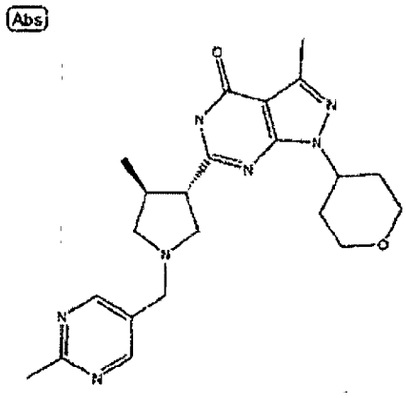
EJEMPLO 93

(a) 3-metil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H ($CDCl_3$) δ 4,85-4,81 (m, 1H), 4,08-4,04 (m, 2H), 3,61-3,55 (m, 2H), 3,31-3,28 (m, 3H), 2,84-2,82 (m, 1H), 2,60-2,53 (m, 2H), 2,49 (s, 3H), 2,29-2,25 (m, 2H), 1,85-1,81 (m, 2H), 1,12 (d, *J*= 6,2 Hz, 3H). EM: (M^+H m/z = 249,1).

(b) 3-metil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

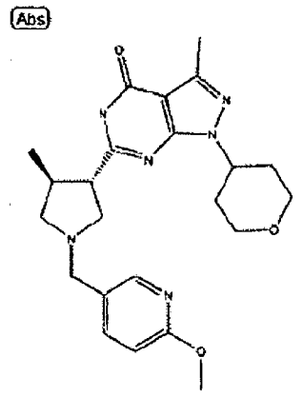


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 3-metil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,63 (s, 2H), 4,74-4,68 (m, 1H), 4,11-4,08 (m, 2H), 3,74-3,63 (m, 2H), 3,60-3,52 (m, 2H), 3,28 (t, *J*= 8,3 Hz, 1H), 3,03 (d, *J*= 9,5 Hz, 1H), 2,85-2,83 (m, 1H), 2,71 (s, 3H), 2,65-2,61 (m, 1H), 2,53 (s, 3H), 2,48-2,29 (m, 2H), 1,98 (t, *J*= 8,7 Hz, 1H),

1,87-1,80 (m, 3H), 1,19 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 424,2).

EJEMPLO 94

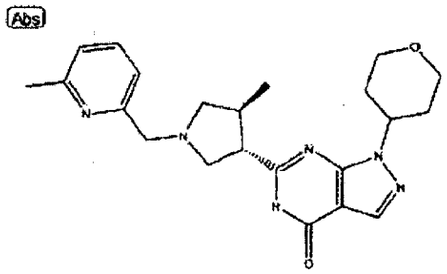
6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 3-metil-6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona y 6-metoxinicotinaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 8,03 (d, *J*= 2,1 Hz, 1H), 7,69 (dd, *J*= 8,7, 2,1 Hz, 1H), 6,78 (d, *J*= 9,1 Hz, 1H), 4,74-4,68 (m, 1H), 4,13-4,07 (m, 2H), 3,89 (s, 3H), 3,70-3,67 (m, 1H), 3,59-3,51 (m, 2H), 3,32 (t, *J*= 8,7 Hz, 1H), 2,97 (d, *J*= 9,9 Hz, 1H), 2,79-2,77 (m, 1H), 2,54 (s, 3H), 2,53-2,50 (m, 1H), 2,41-2,29 (m, 2H), 1,92-1,78 (m, 3H), 1,30-1,18 (m, 2H), 10,86 (t, *J*= 76,6 Hz, 3H). EM: (M^+H m/z 439,2).

EJEMPLO 95

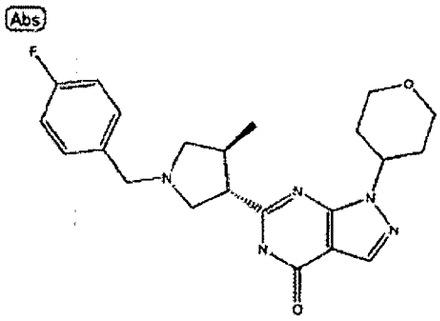
6-{(3S,4S)-4-metil-1-[(6-metilpiridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 6-metilpicolinaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,57 (t, *J*= 7,7 Hz, 1H), 7,20 (d, *J*= 7,9 Hz, 1H), 7,03 (d, *J*= 7,5 Hz, 1H), 4,83-4,77 (m, 1H), 4,13-4,08 (m, 2H), 3,99-3,95 (m, 1H), 3,72-3,69 (m, 1H), 3,62-3,54 (m, 2H), 3,42 (t, *J*= 8,3 Hz, 1H), 3,06 (d, *J*= 9,9 Hz, 1H), 2,85-2,83 (m, 1H), 2,64-2,57 (m, 1H), 2,55 (s, 3H), 2,44-2,29 (m, 3H), 2,08-2,03 (m, 1H), 1,91-1,82 (m, 2H), 1,20 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 409,1).

EJEMPLO 96

6-[(3S,4S)-1-(4-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para

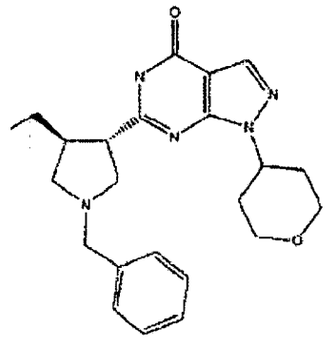
la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 4-fluorobenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,36-7,33 (m, 2H), 7,05-7,01 (m, 2H), 4,82-4,77 (m, 1H), 4,14-4,09 (m, 2H), 3,79-3,76 (m, 1H), 3,62-3,54 (m, 3H), 3,34 (t, *J*= 8,3 Hz, 1H), 2,99 (d, *J*= 9,9 Hz, 1H), 2,85-2,83 (m, 1H), 2,60-2,55 (m, 1H), 2,45-2,30 (m, 3H), 1,99-1,82 (m, 3H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 412,1).

EJEMPLO 97

(a) 6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por (3,4-trans)-1-bencil-4-metilpirrolidin-3-carboxilato de etilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,40-7,26 (m, 5H), 4,78 (m, 1H), 4,12-4,09 (m, 2H), 3,82-3,804 (m, 1H), 3,65-3,54 (m, 3H), 3,35 (t, *J*= 8,3 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,89-2,86 (m, 1H), 2,48-2,32 (m, 3H), 2,20 (m, 1H), 1,95-1,87 (m, 2H), 1,63-1,58 (m, 2H), 1,50-1,49 (m, 1H), 0,93 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 408,1).

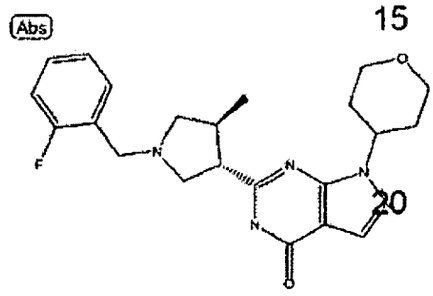
(b) 6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El racemato de 6-[(3,4-trans)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona se separó en una columna de HPLC quiral Chiralcel OJ-H, fase móvil 80/20 CO_2/MeOH, t_R = 3,27, para proporcionar el enantiómero. Analítica: columna AD, fase móvil 85/15 heptano/EtOH, t_R = 12,896. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,40-7,26 (m, 5H), 4,78 (m, 1H), 4,12-4,09 (m, 2H), 3,82-3,804 (m, 1H), 3,65-3,54 (m, 3H), 3,35 (t, *J*= 8,3 Hz, 1H), 2,98 (d, *J*= 9,9 Hz, 1H), 2,89-2,86 (m, 1H), 2,48-2,32 (m, 3H), 2,20 (m, 1H), 1,95-1,87 (m, 2H), 1,63-1,58 (m, 2H), 1,50-1,49 (m, 1H), 0,93 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 408,1).

EJEMPLO 98

6-[(3S,4S)-1-(2-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

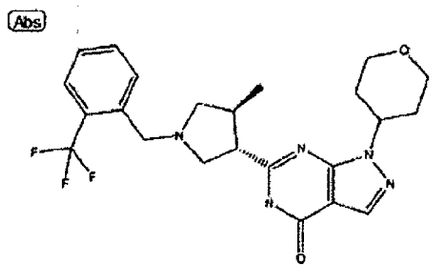


El compuesto del título se proporcionó siguiendo el procedimiento para

la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 2-fluorobenzaldehído. 400 MHz RMN ^{1}H (CD_3OD) δ 7,98 (s, 1H), 7,47-7,42 (m, 1H), 7,33-7,26 (m, 2H), 7,18-7,07 (m, 1H), 4,08-4,04 (m, 2H), 3,85 (s, 2H), 3,69-3,56 (m, 3H), 3,20-2,93 (m, 4H), 2,69-2,62 (m, 1H), 2,40-2,19 (m, 3H), 1,88-1,85 (m, 2H), 1,14 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 412,1).

EJEMPLO 99

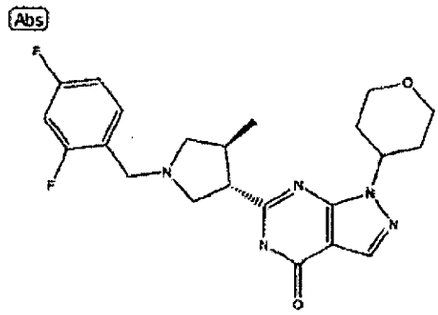
6-{(3S,4S)-4-metil-1-[2-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 2-(trifluorometil)benzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 10,58 (sa, 1H), 8,01 (s, 1H), 7,79-7,76 (m, 1H), 7,64-7,58 (m, 2H), 7,37-7,34 (m, 1H), 4,83-4,76 (m, 1H), 4,14-4,08 (m, 2H), 3,88 (m, 2H), 3,62-3,54 (m, 2H), 3,39 (t, *J*= 8,3 Hz, 1H), 3,02-2,97 (m, 1H), 2,85 (m, 1H), 2,66 (m, 1H), 2,44-2,27 (m, 3H), 2,06-2,03 (m, 1H), 1,91-1,83 (m, 2H), 1,21 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 462,1).

EJEMPLO 100

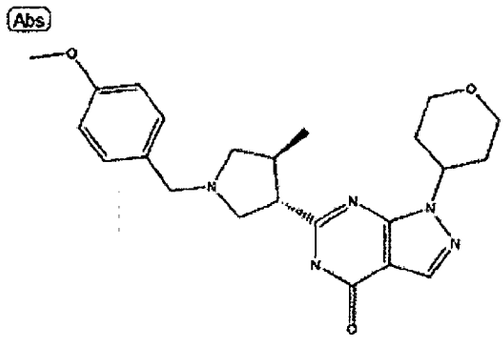
6-[(3S,4S)-1-(2,4-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 2,4-difluorobenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (s, 1H), 7,40-7,38 (m, 2H), 6,90-6,79 (m, 2H), 4,81-4,77 (m, 2H), 4,14-4,08 (m, 2H), 3,88 (m, 2H), 3,62-3,54 (m, 2H), 3,32 (t, *J*= 8,7 Hz, 1H), 3,02 (d, *J*= 9,5 Hz, 1H), 2,86-2,83 (m, 1H), 2,65 (m, 1H), 2,43-2,20 (m, 3H), 2,00-1,83 (m, 2H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 430,2).

EJEMPLO 101

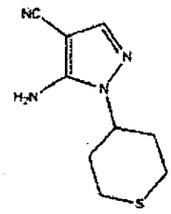
6-[(3S,4S)-1-(4-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 4-metoxibenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (s, 1H), 7,29 (d, *J*= 8,3 Hz, 2H), 6,87 (d, *J*= 8,7 Hz, 2H), 4,82-4,08 (m, 1H), 4,13-4,08 (m, 2H), 3,84-3,75 (m, 4H), 3,61-3,51 (m, 3H), 3,35 (t, *J*= 8,7 Hz, 1H), 2,97 (d, *J*= 9,9 Hz, 1H), 2,82-2,80 (m, 1H), 2,53-2,49 (m, 1H), 2,42-2,30 (m, 3H), 1,95-1,82 (m, 3H), 1,18 (d, *J*= 7,1 Hz, 3H).

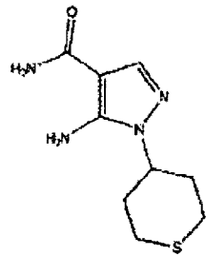
EJEMPLO 102

(a) 5-amino-1-(tetrahidro-2H-tiopiran-4-il)-1H-pirazol-4-carbonitrilo



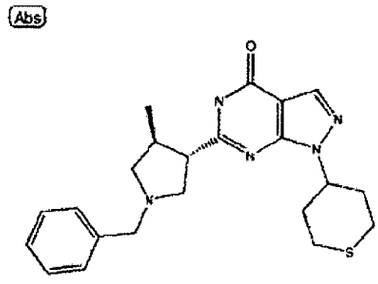
El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carbonitrilo pero sustituyendo por 1-(tetrahidro-2H-tiopiran-4-il)hidrazina. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,44 (s, 1H), 4,71 (s, 2H), 3,84-3,76 (m, 1H), 2,80-2,63 (m, 4H), 2,24-2,10 (m, 4H). EM: (M^+H m/z 209,1).

(b) 5-amino-1-(tetrahidro-2H-tiopiran-4-il)-1H-pirazol-4-carboxamida



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 5-amino-1-(2-metoxifenil)-1H-pirazol-4-carboxamida, pero sustituyendo por 5-amino-1-(tetrahidro-2H-tiopiran-4-il)-1H-pirazol-4-carbonitrilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 7,67 (s, 1H), 4,09-3,97 (m, 1H), 2,89-2,82 (m, 2H), 2,72-2,68 (m, 2H), 2,15-2,10 (m, 4H). EM: (M^+H m/z 227,1).

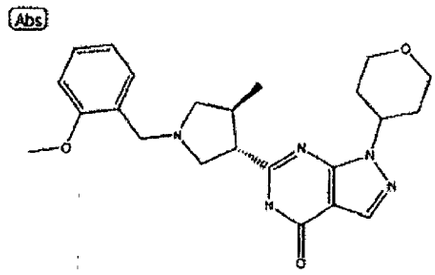
(c) 6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-tiopiran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3,4-trans)-1-bencil-4-metilpirrolidin-3-il]-1-(2-metoxifenil)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por 5-amino-1-(tetrahidro-2H-tiopiran-4-il)-1H-pirazol-4-carboxamida y (3S,4S)-1-bencil-4-metilpirrolidin-3-carboxilato de metilo proporcionó el compuesto del título. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,41-7,26 (m, 5H), 4,60-4,53 (m, 1H), 3,86-3,83 (m, 1H), 3,65 (m, 1H), 3,41-3,37 (m, 1H), 3,02 (m, 1H), 2,94-2,75 (m, 4H), 2,60-2,31 (m, 3H), 2,25-2,16 (m, 2H), 1,99-1,94 (m, 1H), 1,62 (m, 2H), 1,20 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 410,2).

EJEMPLO 103

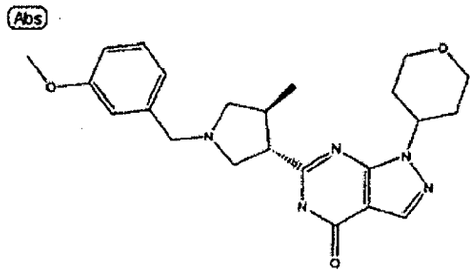
6-[(3S,4S)-1-(2-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 2-metoxibenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,29-7,22 (m, 2H), 6,92-6,88 (m, 2H), 4,83-4,75 (m, 1H), 4,14-4,08 (m, 2H), 3,93 (s, 3H), 3,76-3,69 (m, 2H), 3,62-3,54 (m, 2H), 3,34 (t, *J*= 8,7 Hz, 1H), 3,01 (d, *J*= 9,5 Hz, 1H), 2,78 (m, 1H), 2,56 (m, 1H), 2,41-2,27 (m,3H), 1,92-1,82 (m, 3H), 1,18 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 424,1).

EJEMPLO 104

6-[(3S,4S)-1-(3-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

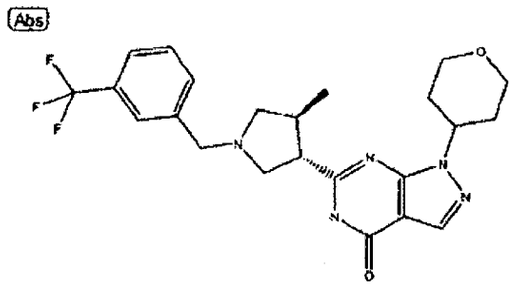


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero

sustituyendo por cianoborohidruro de sodio y 3-metoxibenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,27-7,21 (m, 1H), 6,96-6,92 (m, 2H), 6,81 (d, *J*= 7,1 Hz, 1H), 4,82-4,76 (m, 1H), 4,14-4,08 (m, 2H), 3,85 (s, 3H), 3,79 (s, 1H), 3,62-3,54 (m, 3H), 3,39 (t, *J*= 8,7 Hz, 1H), 3,00 (d, *J*= 10,3 Hz, 1H), 2,81 (m, 1H), 2,53 (m, 1H), 2,42-2,28 (m, 3H), 1,94-1,82 (m, 3H), 1,20 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 424,1).

EJEMPLO 105

6-{(3S,4S)-4-metil-1-[3-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

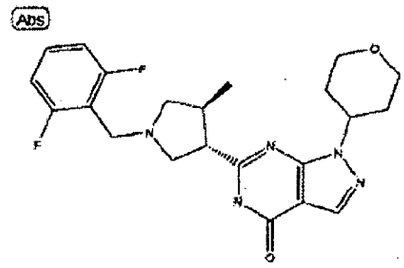


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 3-(trifluorometil)benzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,02 (s, 1H), 7,68-7,63 (m, 1H), 7,55-7,51 (m, 3H), 4,84-4,76 (m, 1H), 4,14-4,08 (m, 2H), 3,87-3,84 (m, 1H), 3,71-3,69 (m, 1H), 3,62-3,54 (m, 2H), 3,36 (t, *J*= 8,3 Hz, 1H), 3,01 (m, 1H), 2,86 (m, 1H), 2,63-2,60 (m, 1H), 2,50-2,27 (m, 3H), 1,98-1,83 (m, 3H), 1,21 (d, *J*= 6,6 Hz, 3H). EM: (M^+H m/z 462,1).

EJEMPLO 106

6-[(3S,4S)-1-(26-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-

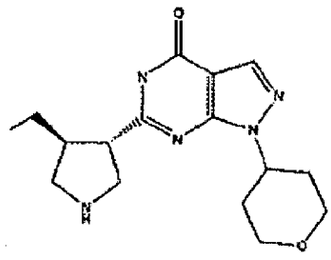
piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por cianoborohidruro de sodio y 2,6-difluorobenzaldehído. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,00 (s, 1H), 7,30-7,22 (m, 1H), 6,96-6,89 (m, 2H), 4,83-4,75 (m, 1H), 4,13-4,08 (m, 2H), 3,91 (s, 2H), 3,62-3,54 (m, 2H), 3,34 (t, *J*= 8,3 Hz, 1H), 3,06 (d, *J*= 9,5 Hz, 1H), 2,80 (m, 1H), 2,66 (m, 1H), 2,40-2,27 (m, 3H), 1,99 (m, 1H), 1,91-1,83 (m, 2H), 1,16 (d, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 430,1).

EJEMPLO 107

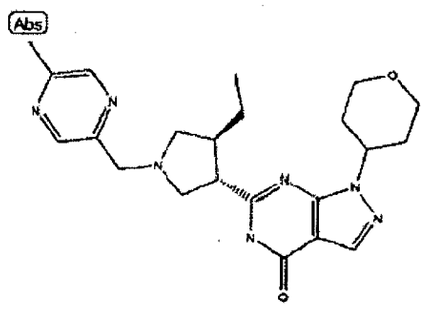
(a) 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-

1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, pero sustituyendo por 6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona. 400 MHz RMN ^{1}H (CD_3OD) δ 8,02 (s, 1H), 4,97 (m, 1H), 4,09-4,06 (m, 2H), 3,78-3,58 (m, 4H), 3,34-3,34 (m, 1H), 3,16-3,11 (m, 1H), 2,68 (d, *J*= 8,7 Hz, 1H), 2,63 (m, 1H), 2,32-2,27 (m, 2H), 1,90-1,87 (m, 2H), 1,69 (m, 1H), 1,57 (m, 1H), 0,97 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z 318,2).

(b) 6-{(3S,4S)-4-etil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

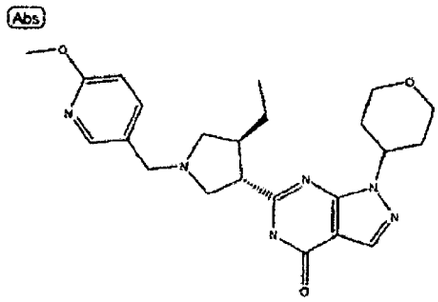


A una disolución de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (4,4 g) en dimetilformamida (62 ml) se añadió ácido acético (2,4 ml), 5-metilpirazin-2-carbaldehído (2 g) y triacetoxiborohidruro de sodio (5,27 g). La mezcla de reacción se agitó durante 2 h a temperatura ambiente y se inactivó cuidadosamente con disolución saturada de bicarbonato sódico, se extrajo 3x con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía MPLC en Biotage eluyendo con 1-4% de metanol/cloruro de metileno/0,5% de hidróxido de amonio saturado proporcionó el compuesto del título (3,9 g). 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,52-8,48 (m, 1H), 8,38 (s, 1H), 8,02 (s, 1H), 4,81-4,75 (m, 1H), 4,11-4,01 (m, 3H), 3,79-3,75 (m, 1H) , 3,60-3,53 (m,

2H), 3,40-3,32 (m, 1H), 3,10-3,08 (m, 1H), 2,94 (m, 1H), 2,63-2,57 (m, 1H), 2,53 (d, *J*= 7,5 Hz, 1H), 2,37-2,18 (m, 4H), 1,90-1,83 (m, 2H), 1,67-1,60 (m, 1H), 1,54-1,47 (m, 1H), 0,95-0,92 (m, 3H). EM: (M^+H m/z 424,2).

EJEMPLO 108

6-{(3S,4S)-4-etil-1-[(6-metoxipiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona

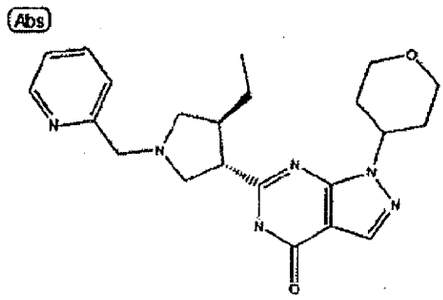


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, cianoborohidruro de sodio y 6-metoxinicotinaldehído. 400 MHz RMN ^1H ($CDCl_3$) δ 8,04 (d, *J*= 2,1 Hz, 1H), 8,02 (s, 1H), 7,73-7,71 (m, 1H), 6,78 (d, *J*= 8,7 Hz, 1H), 4,80-4,75 (m, 1H), 4,12-4,10 (m, 2H), 3,92-3,90 (m, 3H), 3,72-3,70 (m, 1H), 3,61-3,54 (m, 3H), 3,32 (t, *J*= 8,3 Hz, 1H), 2,99 (m, 1H), 2,91 (m, 1H), 2,41 (m, 1H), 2,40-2,28 (m, 2H), 2,21 (m, 1H), 1,95 (m, 1H), 1,91-1,83 (m, 2H), 1,65-1,45 (m, 2H), 0,92 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z 439,2).

EJEMPLO 109

6-[(3S,4S)-4-etil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-

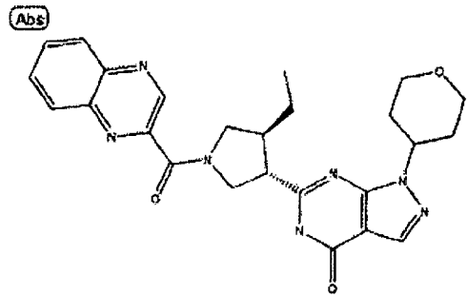
il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (51 mg) en acetonitrilo (1 ml) se añadió carbonato de potasio (88 mg) y bromhidrato de 2-(bromometil)piridina (40 mg) y la mezcla de reacción se calentó a reflujo durante 72 h en un vial cerrado herméticamente. La mezcla de reacción se concentró sobre sílice y se purificó mediante cromatografía ultrarrápida CombiFlash para proporcionar el compuesto del título. 400 MHz RMN ^{1}H ($CDCl_3$) δ 11,50 (sa, 1H), 8,63 (dd, *J*= 1,7, 0,83, Hz, 1H), 8,02 (s, 1H), 7,70-7,67 (m, 1H), 7,40 (d, *J*= 7,9 Hz, 1H), 7,20-7,16 (m, 1H), 4,79-4,77 (m, 1H), 4,12-4,02 (m, 3H), 3,75-3,72 (m, 1H), 3,61-3,53 (m, 2H), 3,39 (t, *J*= 7,9 Hz, 1H), 3,07 (d, *J*= 9,9 Hz, 1H), 2,92-2,90 (m, 1H), 2,37-2,12 (m, 4H), 1,91-1,83 (m, 2H), 1,65-1,60 (m, 1H), 1,54-1,49 (m, 1H), 0,94 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 409,1).

EJEMPLO 110

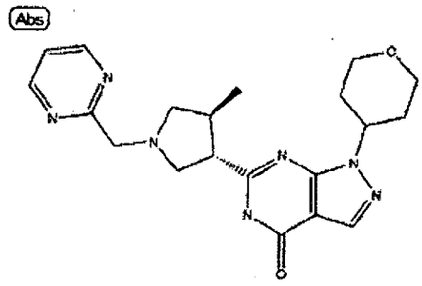
6-[(3S,4S)-4-etil-1-(quinoxalin-2-ilcarbonil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (73 mg) en diclorometano (2 ml) se añadió trietilamina (62 mg) y cloruro de 2-quinoxaloílo (40 mg) a 0ºC. La mezcla de reacción se calentó hasta temperatura ambiente y se agitó durante 18 h. La mezcla de reacción se inactivó con bicarbonato sódico saturado, se extrajo con cloruro de metileno, se secó con sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía ultrarrápida CombiFlash eluyendo con 2-4% de MeOH/cloruro de metileno proporcionó el compuesto del título. 400 MHz RMN ^{1}H ($CDCl_3$) δ 12,78-12,62 (m, 1H), 9,41 (d, *J*= 7,5, Hz, 1H), 8,18-8,00 (m, 3H), 7,87-7,73 (m, 2H), 4,84-4,81 (m, 1H), 4,55-3,86 (m, 6H), 3,61-3,53 (m, 2H), 3,38-3,31 (m, 1H), 2,75 (m, 1H), 2,39-2,34 (m, 2H), 1,93-1,89 (m, 2H), 1,58-1,56 (m, 1H), 1,63-1,50 (m, 1H), 1,01-0,88 (m, 3H). EM: (M^+H m/z 474,2).

EJEMPLO 111

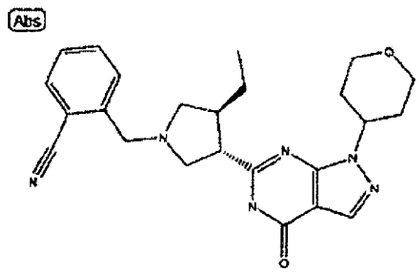
6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona



A una disolución de clorhidrato de 6-[(3S,4S)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona (7,75 g) (véase la preparación en la etapa (a) del ejemplo 73) en dimetilformamida (115 ml) se añadió triflato de hierro (900 mg), clorhidrato de 2-(clorometil)pirimidina (4,5 g) y carbonato de cesio (22,2 g) y la mezcla de reacción se calentó a 60ºC durante 24 h. La mezcla de reacción se concentró sobre gel de sílice y se purificó por cromatografía ultrarrápida eluyendo con 0-15% de metanol/acetato de etilo/1% de hidróxido de amonio saturado para proporcionar el compuesto del título (6 g). 400 MHz RMN ^{1}H ($CDCl_3$) δ 12,30 (sa, 1H), 8,63 (d, *J*= 5,0, Hz, 2H), 8,03 (s, 1H), 7,20 (d, *J*= 5,0, Hz, 1H), 4,84-4,79 (m, 1H), 4,30-4,27 (m, 1H), 4,14-4,08 (m, 2H), 3,87-3,82 (m, 1H), 3,63-3,55 (m, 2H), 3,47 (t, *J*= 7,9 Hz, 1H), 3,29 (d, *J*= 9,9 Hz, 1H), 2,88-2,86 (m, 1H), 2,60-2,56 (m, 1H), 2,46-2,24 (m, 4H), 1,93-1,84 (m, 2H), 1,24 (t, *J*= 7,1 Hz, 3H). EM: (M^+H m/z 396,2).

EJEMPLO 112

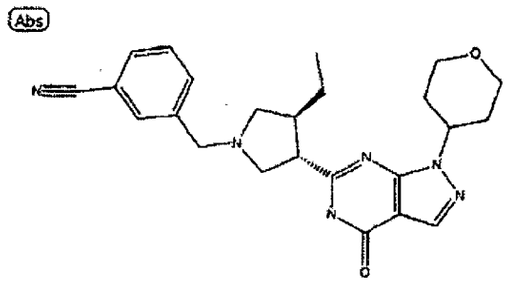
2-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-45-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, cianoborohidruro de sodio y 2-formilbenzonitrilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 11,68 (sa, 1H), 8,01 (s, 1H), 7,68-7,58 (m, 3H), 7,40-7,36 (m, 1H), 4,91 (s, 1H), 4,82-4,76 (m, 1H), 4,12-4,10 (m, 2H), 3,94 (m, 1H), 3,61-6,55 (m, 2H), 3,37 (m, 1H), 3,03-2,94 (m, 2H), 2,66 (m, 1H), 2,41-2,23 (m, 3H), 2,09 (m, 1H), 1,91-1,84 (m, 2H), 1,66-1,49 (m, 2H), 0,93 (t, J= 7,5 Hz, 3H). EM: (M^+H m/z 433,2).

EJEMPLO 113

3-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo

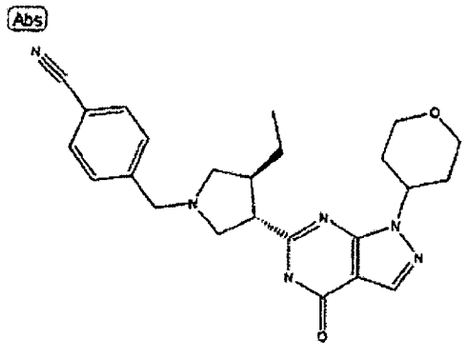


El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-

1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, cianoborohidruro de sodio y 3-formilbenzonitrilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 8,01 (s, 1H), 7,73-7,41 (m, 4H), 4,79 (m, 1H), 4,72 (s, 1H), 4,12-4,09 (m, 2H), 3,82-3,70 (m, 2H), 3,61-3,54 (m, 2H), 3,27 (t, *J*= 8,3 Hz, 1H), 3,02-2,97 (m, 2H), 2,71-2,70 (m, 1H), 2,37-2,30 (m, 2H), 2,20-2,14 (m, 1H), 1,90-1,87 (m, 2H), 1,61-1,60 (m, 1H), 1,51-1,49 (m, 1H), 0,91 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z 433,2).

EJEMPLO 114

4-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-45-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo



El compuesto del título se proporcionó siguiendo el procedimiento para la preparación de 6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona, pero sustituyendo por clorhidrato de 6-[(3S,4S)-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1H-pirazolo[3,4-d]pirimidin-4(5H)-ona, cianoborohidruro de sodio y 4-formilbenzonitrilo. 400 MHz RMN ^{1}H ($CDCl_3$) δ 11,82 (sa, 1H), 8,01 (s, 1H), 7,75 (t, *J*= 7,9 Hz, 1H), 7,59-7,44 (m, 3H), 4,78-4,75 (m, 1H), 4,74 (s, 1H), 4,13-4,08 (m, 2H), 3,77 (m, 1H), 3,70 (m, 1H), 3,61-3,53 (m, 2H), 3,31-3,29 (m, 1H),

3,01-2,90 (m, 2H), 2,58 (m, 1H), 2,37-2,31 (m, 2H), 2,25 (m, 1H), 2,00 (m, 1H), 1,91-1,83 (m, 2H), 1,64-1,63 (m, 1H), 1,61-1,59 (m, 1H), 0,93 (t, *J*= 7,5 Hz, 3H). EM: (M^+H m/z 433,2).

PROTOCOLOS BIOLÓGICOS

La utilidad de los compuestos de fórmula (I), y las sales farmacéuticamente aceptables de los mismos, en el tratamiento o la prevención de enfermedades (tales como se detallan en este documento) en mamíferos (por ejemplo seres humanos) puede demostrarse mediante la actividad de los mismos en ensayos convencionales conocidos para un experto en la materia, incluyendo el ensayo descrito a continuación. Tales ensayos también proporcionan un medio por el cual las actividades de los compuestos de fórmula (I) pueden compararse con las actividades de otros compuestos conocidos.

Actividad inhibidora de fosfodiesterasa 9 (PDE9)

El ensayo de PDE9 se realizó usando el ensayo de proximidad de centelleo (SPA) de fosfodiesterasa (GE Healthcare Life Sciences). El ensayo se llevó a cabo en placas de microtitulación de fondo transparente de 96 pocillos (Costar 3632, Corning Inc). La enzima PDE9 recombinante humana se generó en células SF-9, los sedimentos de células se sonicaron en tampón (TRIS 20 mM, benzamidina 2 mM, EDTA 1 mM, sacarosa 250 mM, PMSF 100 μM, pH 7,5 con HCl), se centrifugaron a 40.000 x g durante 20 min a 4ºC. Los sobrenadantes se almacenaron a -80ºC. Se diluyó fosfato de [8-^{3}H]guanosina 3',5'-cíclico (TRK 392, GE Healthcare Life Sciences) en tampón de ensayo (Tris-HCl 50 mM, pH 7,5, que contenía $MgCl_2$ 1,3 mM) de forma que la concentración final de los pocillos era 50 nM. Los compuestos de prueba se

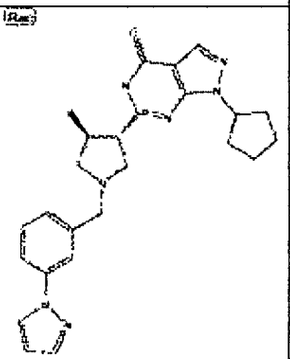
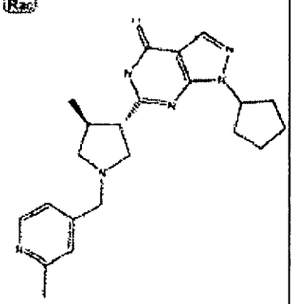
disolvieron en DMSO, se diluyeron en H_2O desionizada (DI) y se diluyeron en serie en 20% de DMSO/80% de H_2O para una concentración final de 2% de DMSO. Para el ensayo, la PDE9 se diluyó con tampón de ensayo de forma que el 20% o menos del sustrato se hidrolizó para dar 5'GMP. Cada pocillo de ensayo contenía 10 µl del compuesto de prueba o disolvente, 40 µl de [^{3}H]GMPc y 50 µl de enzima, el valor de fondo se determinó mediante una alta concentración de un inhibidor de PDE. El ensayo se inició con la adición de la enzima y se llevó a cabo a temperatura ambiente durante 30 min. El ensayo se terminó con la adición de 10 µl de un inhibidor de PDE9 que era suficiente para inhibir totalmente la actividad enzimática, inmediatamente seguido por la adición de 50 µl por pocillo de perlas de SPA. Las placas se cerraron herméticamente, se removieron con vórtex, se dejaron reposar durante >300 min, luego se contaron en un Wallac TriLux MicroBeta LSC.

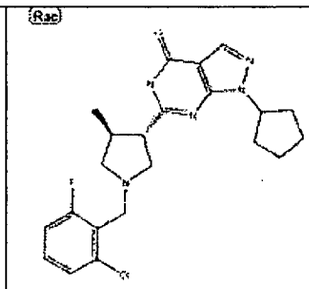
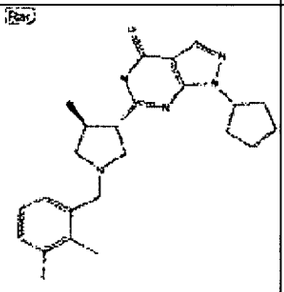
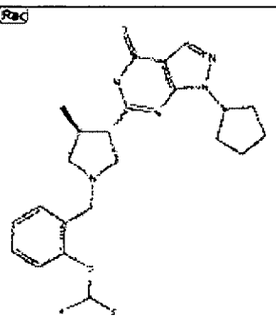
Nº de ejemplo	G5678A (U):CI50	Nº de ejemplo	G5678A (U):CI50	Nº de ejemplo	G5678A (U):CI50
3	9,46 nM	43	36,4 nM	80	3,72 nM
4	624 nM	44	10,9 nM	81	2,92 nM
5	558 nM	45	38,7 nM	82	5,18 nM
6	57,1 nM	46	8,53 nM	83	24,5 nM
7	11,6 nM	47	5,53 nM	84	1,87 nM
8	11,2 nM	48	40,7 nM	85	0,903
9	2,84 nM	49	4,55 nM	86	1,44 nM
10	4,98 nM	50	125 nM	87	5,72 nM
11	18,9 nM	51	8,19 nM	88	17,9 nM

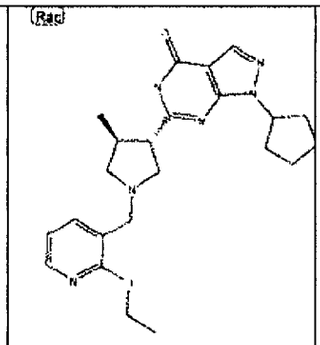
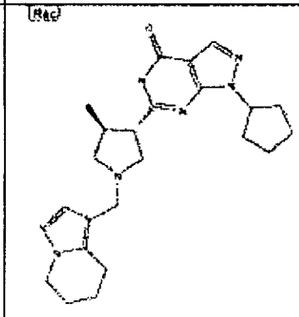
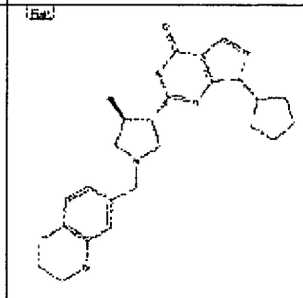
12	7,23 nM	52	26,0 nM	89	1,70 nM
13	6,61 nM	53	7,30 nM	90	1,41 nM
14	26,0 nM	54	14,7 nM	91	6,69 nM
17	16,2 nM	55	6,55 nM	92	23,3 nM
18	8,26 nM	56	4,81 nM	93	24,3 nM
19	2,68 nM	57	122 nM	94	14,2 nM
20	7,06 nM	58	334 nM	95	3,92 nM
21	34,5 nM	59	7,37 nM	96	7,13 nM
22	43,6 nM	60	44,8 nM	97(a)	7,20 nM
23	1,32 nM	61	7,35 nM	97(b)	5,56 nM
24	119 nM	62	520 nM	98	7,93 nM
25	9,07 nM	63	123 nM	99	12,8 nM
26	11,4 nM	64	873 nM	100	22,7 nM
27	7,45 nM	65	17,1 nM	101	7,94 nM
28	6,86 nM	66	18,1 nM	102	19,7 nM
29	2,17 nM	67	9,74 nM	103	15,2 nM
31	23,2 nM	68	36,7 nM	104	3,98 nM
32	5,19 nM	69	30,7 nM	105	3,29 nM
33	6,29 nM	70	10,2 nM	106	8,06 nM
34	4,33 nM	71	16,1 nM	107	4,33 nM
35	53,8 nM	72	40,1 nM	108	3,11 nM
36	5,08 nM	73	6,01 nM	109	4,21 nM
37	3,23 nM	74	6,14 nM	110	2,59 nM
38	5,75 nM	75	5,46 nM	111	12,5 nM

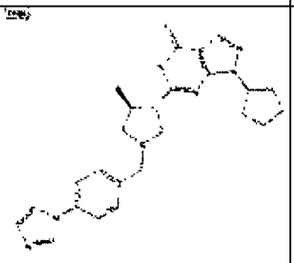
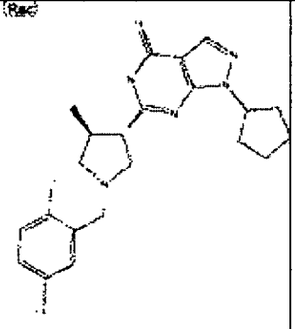
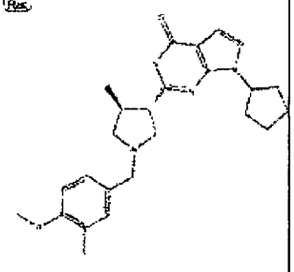
39	58,1 nM	76	3,50 nM	112	1,37 nM
40	44,5 nM	77	1,24 nM	113	<1,00
41	63,8 nM	78	4,35 nM	114	2,31 nM
42	268 nM	79	3,72 nM		

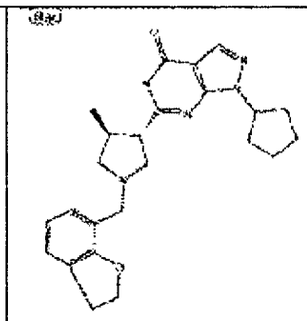
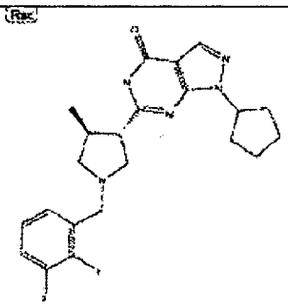
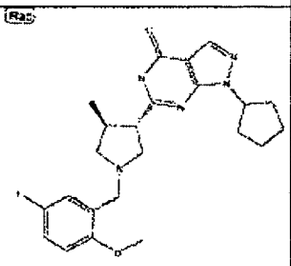
Los siguientes compuestos adicionales se prepararon según los procedimientos expuestos anteriormente:

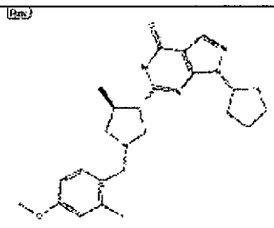
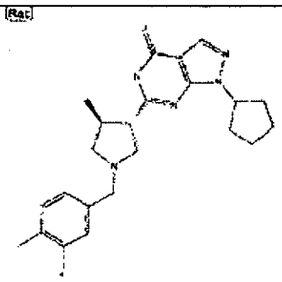
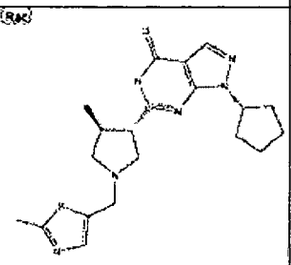
Nº de ejemplo	Estructura	Nombre IUPAC	G5678A (U):CI50	Masa exacta	Peso molec.	m/z (M+1)obs.	Tiempo de retención
115		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[3-(1H-pirazol-1-il) bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	40,4 nM	443,243	557,579	444,28	2,71
116		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpiridin-4-il) metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	34,0 nM	392,233	620,556	393,32	2,04

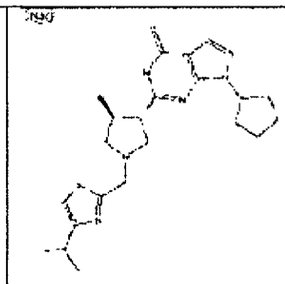
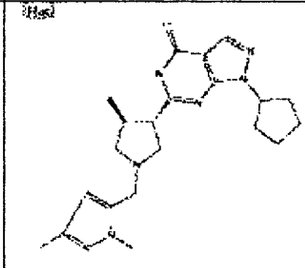
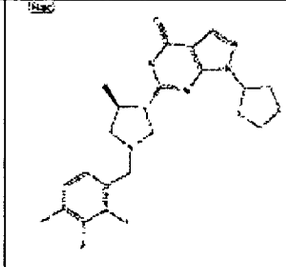
117		6-[(3,4-trans)-1-(2-cloro-6-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	126 nM	429,173	543,951	430,23	2,7
118		1-ciclopentil-6-[(3,4-trans)-1-(2,3-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	74 nM	405,253	519,57	406,32	2,9
119		1-ciclopentil-6-{(3,4-trans)-1-[2-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	32,8 nM	443,213	557,522	444,28	2,82

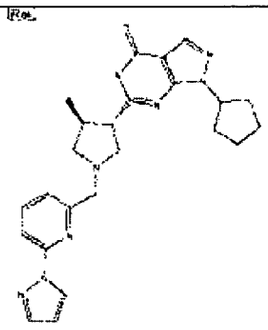
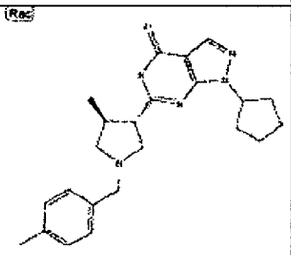
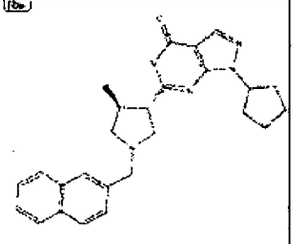
120		1-ciclopentil-6-{(3,4-trans)-1-[(2-etoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	62,7 nM	422,243	650,582	423,3	2,66
121		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,5,6,7-tetrahidropirazolo[1,5-a]piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	83,9 nM	421,259	535,573	422,33	2,43
122		1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1,4-benzodioxin-6-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	56,4 nM	435,227	549,552	436,28	2,68

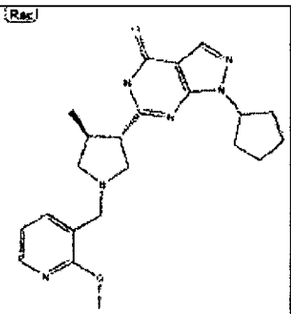
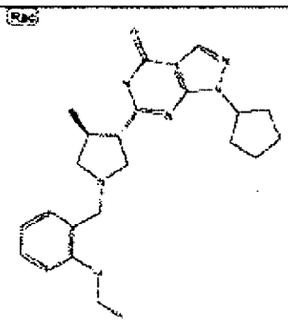
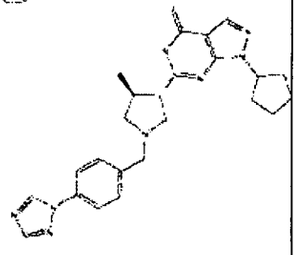
		4-ona					
123		1-ciclopentil-6-{{3,4-trans)-1-[4-(1H-imidazol-1-il)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	39,3 nM	443,243	557,579	444,29	2,11
124		1-ciclopentil-6-[(3,4-trans)-1-(2,5-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	80,9 nM	445,144	560,406	446,19	2,92
125		1-ciclopentil-6-[(3,4-trans)-1-(4-metoxi-3-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	55,2 nM	421,248	535,569	422,31	2,89

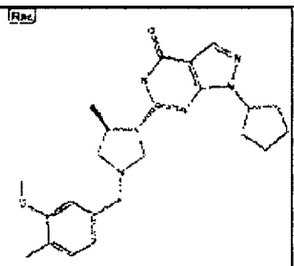
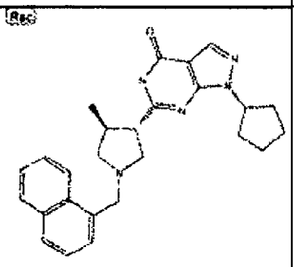
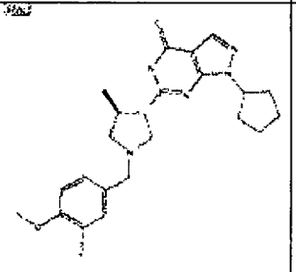
126		1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1-benzofuran-7-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	88,7 nM	419,232	533,553	420,31	2,75
127		1-ciclopentil-6-[(3,4-trans)-1-(2,3-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	61,7 nM	413,203	527,496	414,28	2,73
128		1-ciclopentil-6-[(3,4-trans)-1-(5-fluoro-2-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	70,9 nM	425,223	539,532	426,29	2,8

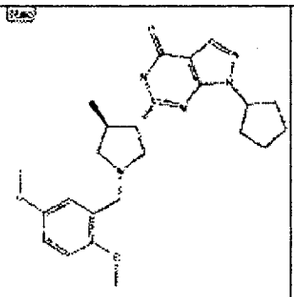
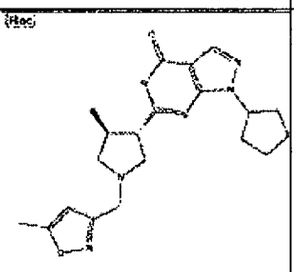
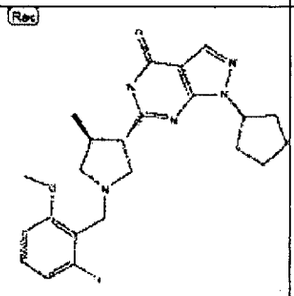
129		1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-4-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	71,8 nM	425,223	539,532	426,29	2,75
130		1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	60,0 nM	409,228	523,533	410,28	2,87
131		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metil-1,3-tiazol-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	41,9 nM	398,189	512,557	399,23	2,32

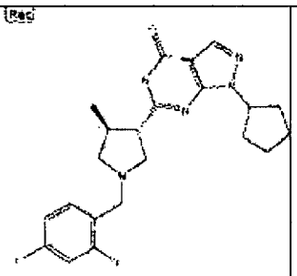
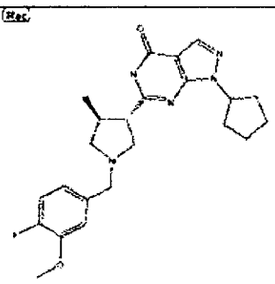
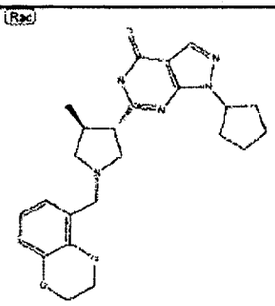
132		1-ciclopentil-6-{(3,4-trans)-1-[(4-isopropil-1,3-tiazol-2-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	37,5 nM	426,22	540,611	427,28	2,83
133		1-ciclopentil-6-{(3,4-trans)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	33,7 nM	395,243	509,535	396,31	2,35
134		1-ciclopentil-6-[(3,4-trans)-1-(2,3-difluoro-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	93,5 nM	427,218	541,523	428,29	2,89

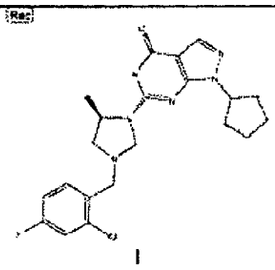
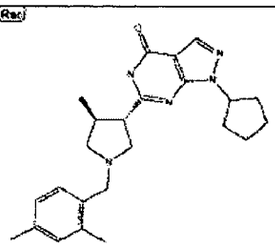
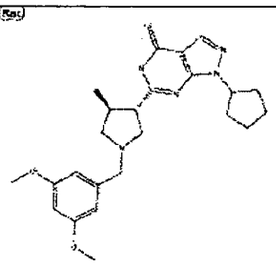
135		1-ciclopentil-6-[(3,4-trans)-4-metil-1-{[6-(1H-pirazol-1-il)piridin-2-il]metil}pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	91,6 nM	444,239	672,592	445,3	2,59
136		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	132 nM	391,237	505,543	392,31	2,81
137		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-naftilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	54,5 nM	427,237	541,576	428,3	2,97

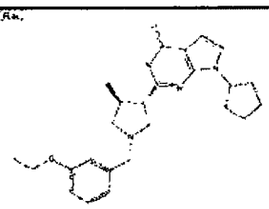
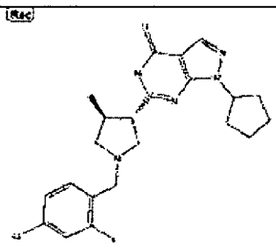
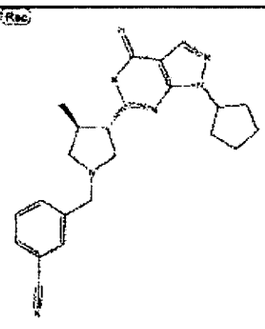
138		1-ciclopentil-6-{(3,4-trans)-1-[(2-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	47,7 nM	408,227	636,555	409,29	2,5
139		1-ciclopentil-6-[(3,4-trans)-1-(2-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	97,5 nM	421,248	535,569	422,33	2,88
140		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(1H-1,2,4-triazol-1-il)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	26,8 nM	444,239	558,567	445,3	2,42

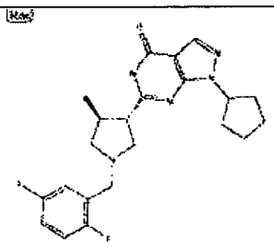
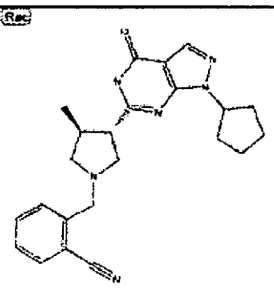
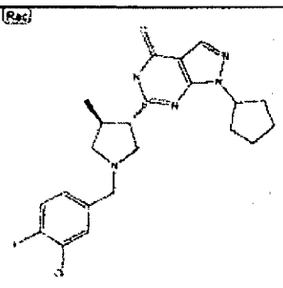
141		1-ciclopentil-6-[(3,4-trans)-1-(3-metoxi-4-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	53,1 nM	421,248	535,569	422,3	2,94
142		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(1-naftilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	47,5 nM	427,237	541,576	428,3	2,93
143		1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-4-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	35,1 nM	425,223	539,532	426,29	2,73

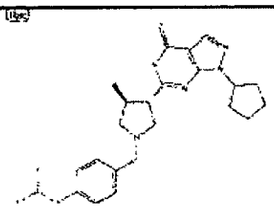
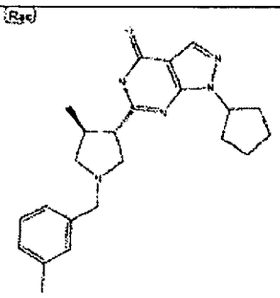
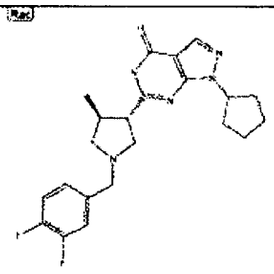
144		1-ciclopentil-6-[(3,4-trans)-1-(2,5-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	99,6 nM	437,243	551,568	438,29	2,79
145		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(5-metilisoxazol-3-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	77,4 nM	382,212	496,492	383,27	2,5
146		1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-6-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	165 nM	425,223	539,532	426,29	2,76

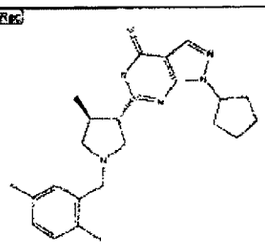
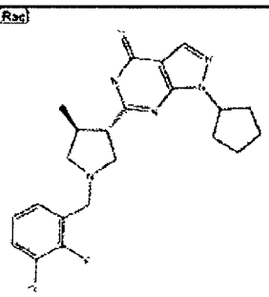
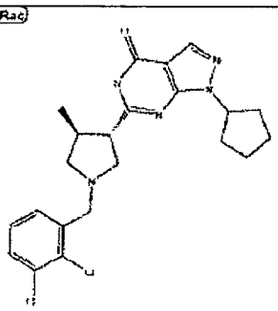
147		1-ciclopentil-6-[(3,4-trans)-1-(2,4-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	79,8 nM	413,203	527,496	414,28	2,72
148		1-ciclopentil-6-[(3,4-trans)-1-(4-fluoro-3-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	36,0 nM	425,223	539,532	426,29	2,79
149		1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1,4-benzodioxin-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	47,1 nM	435,227	549,552	436,28	2,73

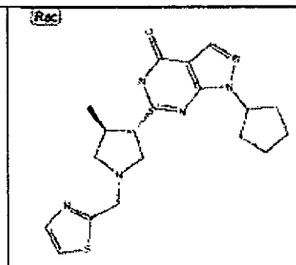
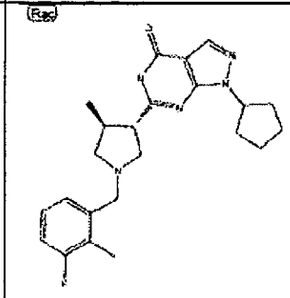
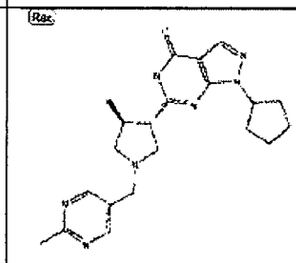
150		6-[(3,4-trans)-1-(2-cloro-4-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	93,5 nM	429,173	543,951	430,23	2,82
151		1-ciclopentil-6-[(3,4-trans)-1-(2,4-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	117 nM	405,253	519,57	406,32	2,92
152		1-ciclopentil-6-[(3,4-trans)-1-(3,5-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	42,2 nM	437,243	551,568	438,29	2,8

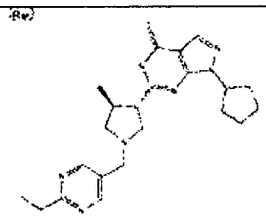
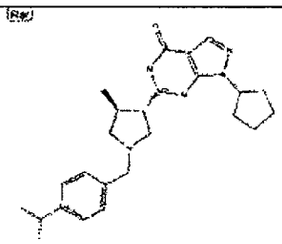
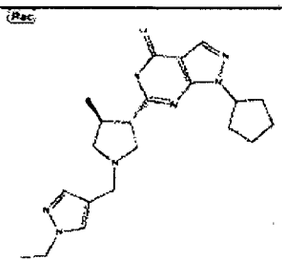
153		1-ciclopentil-6-[(3,4-trans)-1-(3-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	54,4 nM	421,248	535,569	422,28	2,88
154		6-[(3,4-trans)-1-(4-cloro-2-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	175 nM	429,173	543,951	430,23	2,88
155		3-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo	27,9 nM	402,217	516,526	403,25	2,61

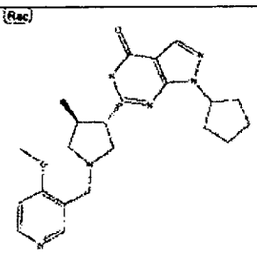
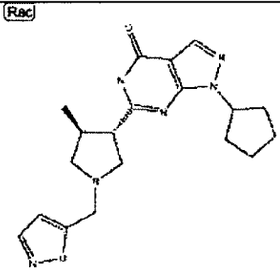
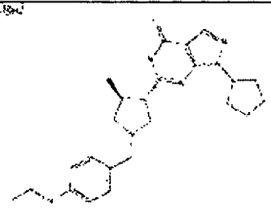
156		1-ciclopentil-6-[(3,4-trans)-1-(2,5-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	40,8 nM	413,203	527,496	414,27	2,69
157		2-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo	56,4 nM	402,217	516,526	403,26	2,6
158		6-[(3,4-trans)-1-(3-cloro-4-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	50,9 nM	429,173	543,951	430,21	2,91

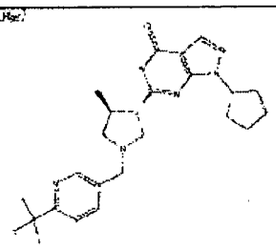
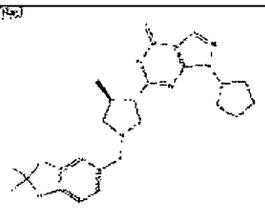
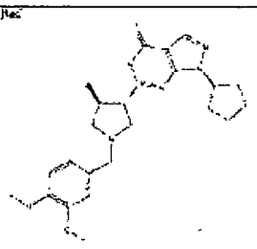
159		1-ciclopentil-6-{(3,4-trans)-1-[4-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	59,9 nM	443,213	557,522	444,26	2,88
160		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(3-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	43,4 nM	391,237	505,543	392,29	2,8
161		1-ciclopentil-6-[(3,4-trans)-1-(3,4-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	40,4 nM	413,203	527,496	414,26	2,8

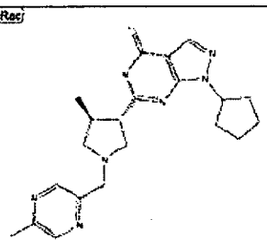
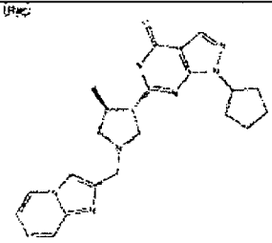
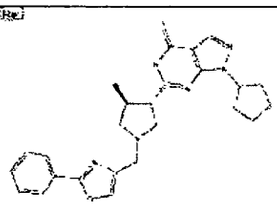
162		1-ciclopentil-6-[(3,4-trans)-1-(2,5-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	60,1 nM	405,253	519,57	406,32	2,92
163		6-[(3,4-trans)-1-(3-cloro-2-fluorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	53,4 nM	429,173	543,951	430,22	2,85
164		1-ciclopentil-6-[(3,4-trans)-1-(2,3-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	78,9 nM	445,144	560,406	446,15	2,94

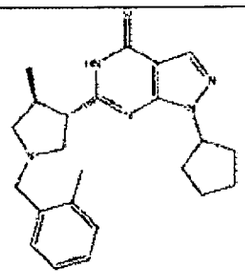
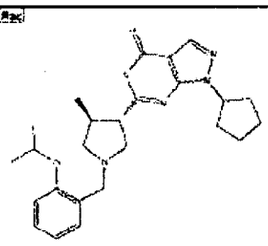
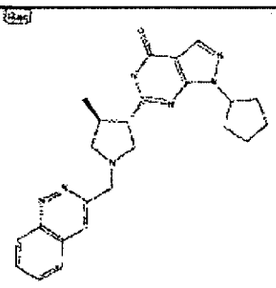
165		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(1,3-tiazol-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	54,2 nM	384,173	498,53	385,22	2,35
166		1-ciclopentil-6-[(3,4-trans)-1-(3-fluoro-2-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	68,3 nM	409,228	523,533	410,26	2,83
167		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	40,7 nM	393,228	507,519	394,3	2,21

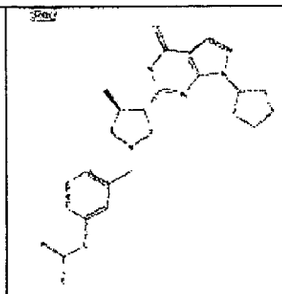
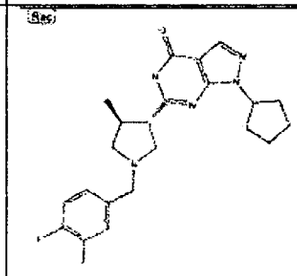
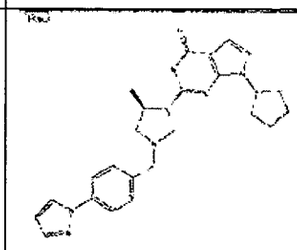
168		1-ciclopentil-6-{(3,4-trans)-1-[(2-etilpirimidin-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	30,7 nM	407,243	521,546	408,31	2,36
169		1-ciclopentil-6-[(3,4-trans)-1-(4-isopropilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	117 nM	419,269	533,597	420,34	3,1
170		1-ciclopentil-6-{(3,4-trans)-1-[(1-etil-1H-pirazol-4-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	74,6 nM	395,243	509,535	396,31	2,37

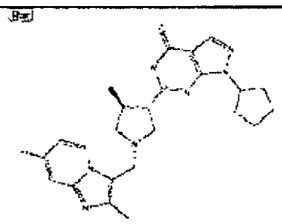
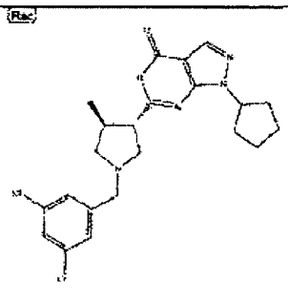
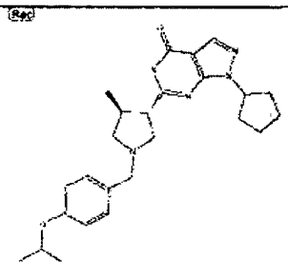
171		1-ciclopentil-6-{(3,4-trans)-1-[(4-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	51,3 nM	408,227	636,555	409,29	2,05
172		1-ciclopentil-6-[(3,4-trans)-1-(isoxazol-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	67,0 nM	368,196	482,465	369,25	2,29
173		1-ciclopentil-6-[(3,4-trans)-1-(4-etoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	64,0 nM	421,248	535,569	422,29	2,85

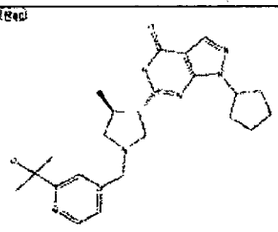
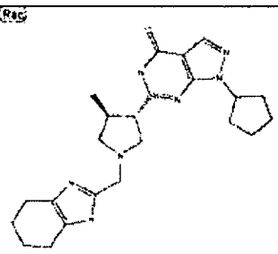
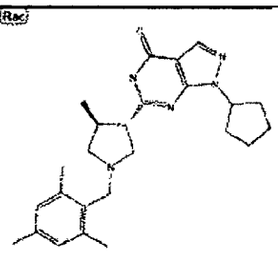
174		1-ciclopentil-6-[(3,4-trans)-1-{[6-(1-hidroxi-1-metiletil)piridin-3-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	42,0 nM	436,259	664,609	437,32	2,14
175		1-ciclopentil-6-{(3,4-trans)-1-[(2,2-dimetil-2,3-dihidro-1-benzofuran-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	74,8 nM	447,264	561,607	448,3	2,96
176		1-ciclopentil-6-[(3,4-trans)-1-(3,4-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-	27,1 nM	437,243	551,568	438,29	2,59

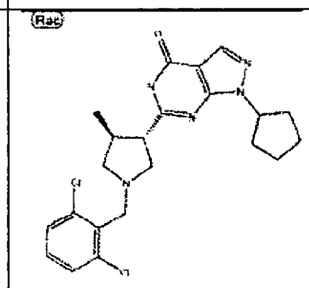
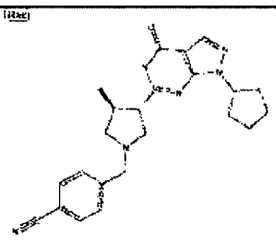
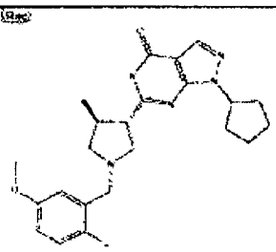
		d]pirimidin-4-ona					
177		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	42,2 nM	393,228	507,519	394,3	2,32
178		1-ciclopentil-6-[(3,4-trans)-1-(imidazo[1,2-a]piridin-2-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	44,7 nM	417,228	531,541	418,27	2,14
179		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-fenil-1,3-oxazol-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	47,2 nM	444,227	558,563	445,27	2,88

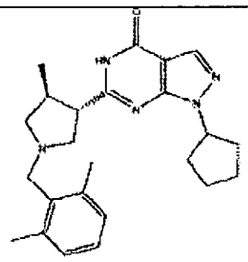
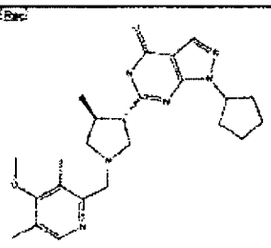
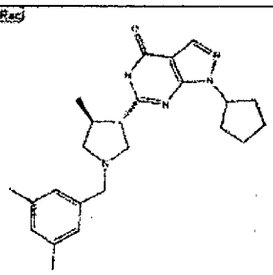
		4-ona					
180		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(2-metilbencil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	83,8 nM	391,237	505,543	392,3	2,77
181		1-ciclopentil-6-[(3,4-trans)-1-(2-isopropoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	134 nM	435,264	549,596	436,33	3
182		6-[(3,4-trans)-1-(cinolin-3-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	22,5 nM	429,228	543,552	430,26	2,53

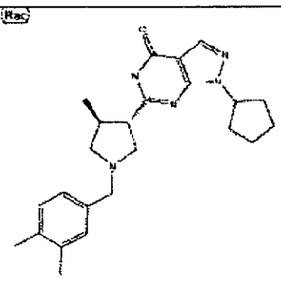
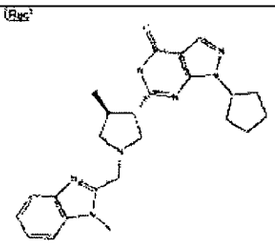
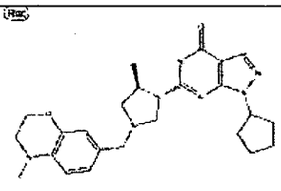
183		1-ciclopentil-6-{(3,4-trans)-1-[3-(difluorometoxi)bencil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	29,8 nM	443,213	557,522	444,26	2,87
184		1-ciclopentil-6-[(3,4-trans)-1-(4-fluoro-3-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	90,0 nM	409,228	523,533	410,26	2,87
185		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(1H-pirazol-1-il)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	33,5 nM	443,243	557,579	444,27	2,69

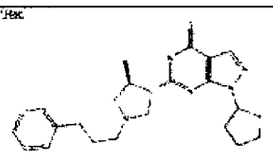
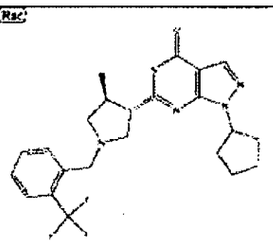
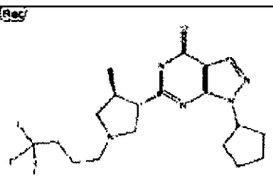
186		1-ciclopentil-6-{(3,4-trans)-1-[(2,7-dimetilimidazo[1,2-a]piridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	155 nM	445,259	559,595	446,27	2,19
187		1-ciclopentil-6-[(3,4-trans)-1-(3,5-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	70,9 nM	445,144	560,406	446,16	3,04
188		1-ciclopentil-6-[(3,4-trans)-1-(4-isopropoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	72,7 nM	435,264	549,596	436,3	2,98

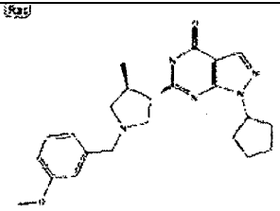
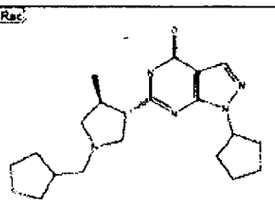
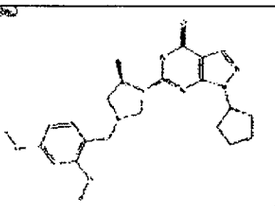
189		1-ciclopentil-6-[(3,4-trans)-1-{[2-(1-hidroxi-1-metiletil)piridin-4-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	23,7 nM	436,259	664,609	437,21	2,13
190		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,5,6,7-tetrahidro-1,3-benzotiazol-2-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	55,4 nM	438,22	552,622	439,27	2,81
191		1-ciclopentil-6-[(3,4-trans)-1-(mesitilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-	198 nM	419,269	533,597	420,34	3

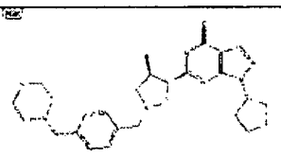
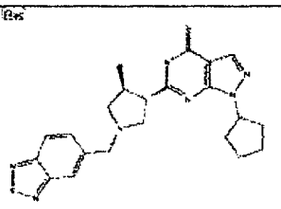
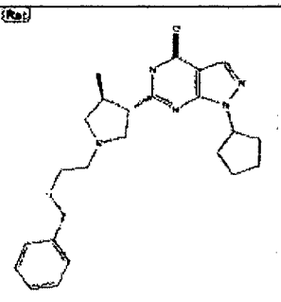
		d]pirimidin-4-ona					
192		1-ciclopentil-6-[(3,4-trans)-1-(2,6-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	236 nM	445,144	560,406	446,14	2,75
193		4-{[(3,4-trans)-3-(1-ciclopentil-4-oxo-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il)-4-metilpirrolidin-1-il]metil}benzonitrilo	57,7 nM	402,217	516,526	403,25	2,61
194		1-ciclopentil-6-[(3,4-trans)-1-(2-fluoro-5-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	54,7 nM	425,223	539,532	426,29	2,75

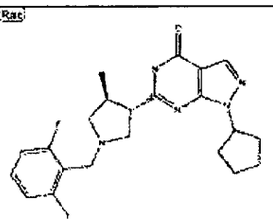
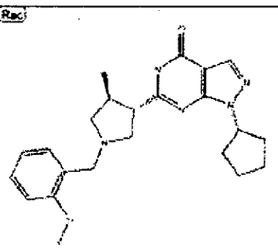
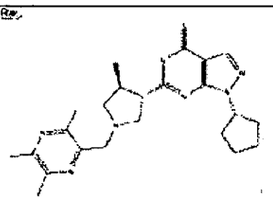
		4-ona					
195		1-ciclopentil-6-[(3,4-trans)-1-(2,6-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	198 nM	405,253	519,57	406,31	2,83
196		1-ciclopentil-6-{(3,4-trans)-1-[(4-metoxi-3,5-dimetilpiridin-2-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	187 nM	436,259	664,609	437,32	2,76
197		1-ciclopentil-6-[(3,4-trans)-1-(3,5-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	53,5 nM	405,253	519,57	406,33	2,96

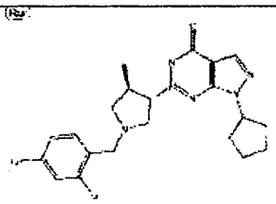
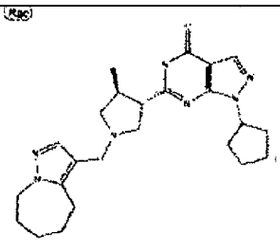
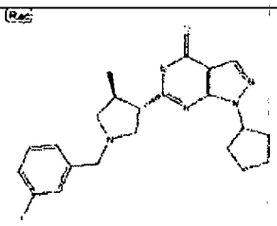
198		1-ciclopentil-6-[(3,4-trans)-1-(3,4-dimetilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	93,6 nM	405,253	519,57	406,31	2,94
199		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(1-metil-1H-bencimidazol-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	35,3 nM	431,243	545,568	432,29	2,64
200		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(4-metil-3,4-dihidro-2H-1,4-benzoxazin-7-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-	176 nM	448,259	676,62	{449,3}	{2,78}

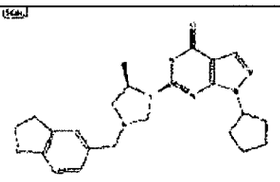
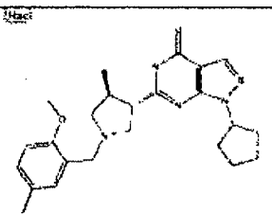
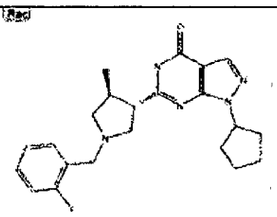
		pirazolo[3,4-d]pirimidin-4-ona					
201		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(3-fenilpropil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	146 nM	405,253	519,57	{406,3}	{2,93}
202		1-ciclopentil-6-[(3,4-trans)-4-metil-1-[2-(trifluorometil)bencil]-pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	104 nM	445,209	559,513	{446,2}	{2,9}
203		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(4,4,4-trifluorobutil) pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	83,7 nM	397,209	511,469	{398,2}	{2,69}

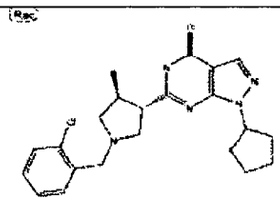
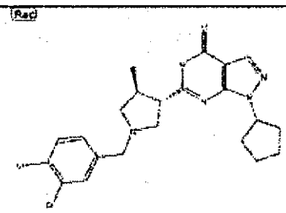
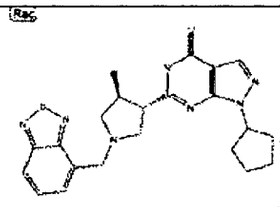
		4-ona					
204		1-ciclopentil-6-[(3,4-trans)-1-(3-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	9,56 nM	407,232	521,542	{408,3}	{2,74}
205		1-ciclopentil-6-[(3,4-trans)-1-(ciclopentilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	286 nM	369,253	483,537	{370,2}	{2,72}
206		1-ciclopentil-6-[(3,4-trans)-1-(2,4-dimetoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	68,4 nM	437,243	551,568	{438,2}	{2,82}

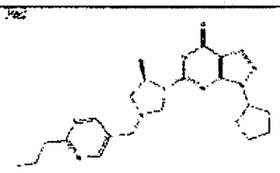
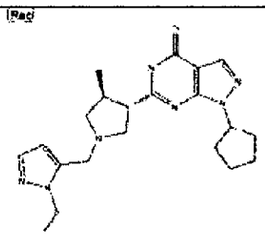
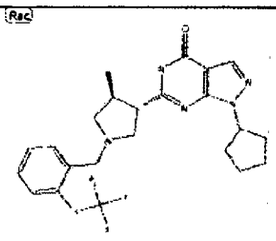
207		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(morfolin-4-ilmetil)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	46,2 nM	476,29	590,649	{477,3; 477,3}	{1,94; 2,17}
208		6-[(3,4-trans)-1-(2,1,3-benzotiadiazol-5-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	7,13 nM	435,184	549,578	{436,2}	{2,66}
209		6-{(3,4-trans)-1-[2-(benciloxi)etil]-4-metilpirrolidin-3-il}-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	52,9 nM	421,248	535,569	{422,2}	{2,85}

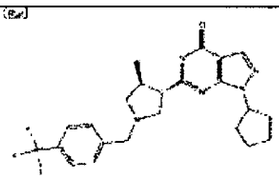
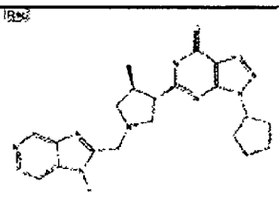
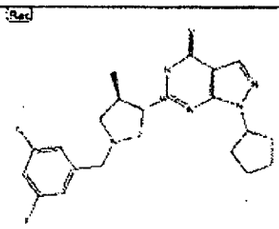
		4-ona					
210	(Rac) 	1-ciclopentil-6-[(3,4-trans)-1-(2,6-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	16,2 nM	413,203	527,496	{414,2}	{2,62}
211	(Rac) 	1-ciclopentil-6-[(3,4-trans)-1-(2-metoxibencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d}pirimidin-4-ona	39,8 nM	407,232	521,542	{408,2}	{2,76}
212	(Rac) 	1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(3,5,6-trimetilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	9,98 nM	421,259	535,573	{422,3}	{2,51}

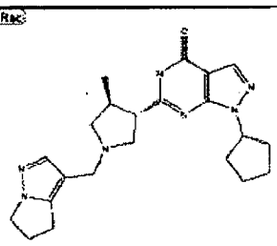
213		1-ciclopentil-6-[(3,4-trans)-1-(2,4-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	124 nM	445,144	560,406	{446,1}	{2,98}
214		1-ciclopentil-6-[(3,4-trans)-4-metil-1-(5,6,7,8-tetrahidro-4H-pirazolo[1,5-a]azepin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	15,7 nM	435,275	549,6	{436,3}	{2,59}
215		1-ciclopentil-6-[(3,4-trans)-1-(3-fluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	11,5 nM	395,212	509,506	{396,2}	{2,73}

		4-ona					
216		1-ciclopentil-6-[(3,4-trans)-1-(2,3-dihidro-1-benzofuran-5-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	17,4 nM	419,232	533,553	{420,2}	{2,71}
217		1-ciclopentil-6-[(3,4-trans)-1-(2-metoxi-5-metilbencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	25,0 nM	421,248	535,569	{422,3}	{2,91}
218		1-ciclopentil-6-[(3,4-trans)-1-(2-fluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	15,6 nM	395,212	509,506	{396,2}	{2,67}

219		6-[(3,4-trans)-1-(2-clorobencil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	48,4 nM	411,183	525,961	{412,2}	{2,78}
220		1-ciclopentil-6-[(3,4-trans)-1-(3,4-diclorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4 H-pirazolo[3,4-d]pirimidin-4-ona	28,0 nM	445,144	560,406	{446,1}	{3,04}
221		6-[(3,4-trans)-1-(2,1,3-benzotiadiazol-4-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-	12,7 nM	435,184	549,578	{436,2}	{2,67}

		4-ona					
222		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(2-propilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	6,03 nM	421,259	535,573	{422,3}	{2,52}
223		1-ciclopentil-6-{(3,4-trans)-1-[(1-etil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	14,4 nM	395,243	509,535	{396,3}	{2,39}
224		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[2-(trifluorometoxi)bencil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	116 nM	461,204	575,512	{462,2}	{2,96}

225		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[4-(trifluorometil)bencil]-pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	34,9 nM	445,209	559,513	{446,2}	{3,01}
226		1-ciclopentil-6-{(3,4-trans)-4-metil-1-[(1-metil-1H-imidazo[4,5-c]piridin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	3,78 nM	432,239	660,581	{433,2}	{2,03}
227		1-ciclopentil-6-[(3,4-trans)-1-(3,5-difluorobencil)-4-metilpirrolidin-3-il]-1,5-dihidro-4 H-pirazolo[3,4-d]pirimidin-4-ona	7,42 nM	413,203	527,496	{414,2}	{2,79}

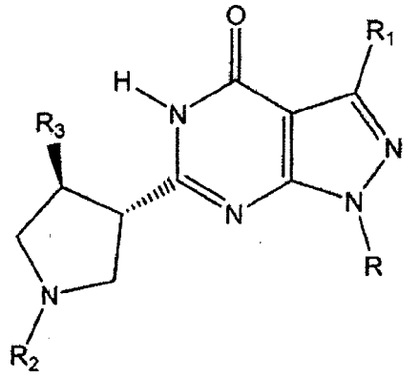
228		1-ciclopentil-6-[(3,4-trans)-1-(5,6-dihidro-4H-pirrolo[1,2-b]pirazol-3-ilmetil)-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona	49,1 nM	407,243	521,546	{408,3}	{2,37}

Aunque en este documento se han descrito ciertas realizaciones actualmente preferidas de la invención, para aquellos expertos en la materia a la que la invención se refiere será evidente que pueden hacerse variaciones y modificaciones de las realizaciones descritas sin apartarse del espíritu y el alcance de la invención. Por consiguiente, se pretende que la invención se limite sólo hasta el grado requerido por las reivindicaciones adjuntas y las normas jurídicas aplicables.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes:

REIVINDICACIONES

1. Un compuesto de fórmula (I),



(I)

o una sal farmacéuticamente aceptable del mismo, en la que:

R se selecciona del grupo que está constituido por alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), cicloalquilo (C_3-C_8), heterocicloalquilo, arilo y heteroarilo, cada uno de los cuales puede estar opcionalmente sustituido con de uno a tres sustituyentes, seleccionándose independientemente los sustituyentes del grupo que está constituido por alquilo (C_1-C_4), alcoxi (C_1-C_4), halo y haloalquilo (C_1-C_4);

R_1 se selecciona del grupo que está constituido por hidrógeno, alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), haloalquilo (C_1-C_4) y ciclopropilo;

R_2 se selecciona del grupo que está constituido por alquilo (C_1-C_6), alquenilo (C_2-C_6), alquinilo (C_2-C_6), haloalquilo (C_1-C_6), heteroarilo seleccionado del grupo que está constituido por piridinilo, piridazinilo, pirimidinilo y pirazinilo, y ER_5, en el que el heteroarilo puede estar opcionalmente sustituido con de uno a tres sustituyentes independientemente seleccionados del grupo que está

constituido por alquilo (C_1-C_4) y haloalquilo (C_1-C_4);

R_3 se selecciona del grupo que está constituido por hidrógeno, alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), cicloalquilo (C_3-C_6) y haloalquilo (C_1-C_4);

E se selecciona del grupo que está constituido por $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ y -C(O)-;

R_5 se selecciona del grupo que está constituido por cicloalquilo (C_3-C_8), heterocicloalquilo, arilo, ariloxi y heteroarilo, cualquiera de los cuales puede estar opcionalmente sustituido con de uno a tres sustituyentes, seleccionándose independientemente tales sustituyentes del grupo que está constituido por alquilo (C_1-C_4), alquenilo (C_2-C_4), alquinilo (C_2-C_4), hidroxialquilo (C_1-C_4), haloalquilo (C_1-C_4), alcoxi (C_1-C_4), haloalcoxi (C_1-C_4), cicloalquilo (C_3-C_8), halo, ciano, fenilo, morfolinilo, alquil (C_1-C_4)-amino, pirazolilo, triazolilo e imidazolilo.

2. El compuesto de la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en el que:

R se selecciona del grupo que está constituido por etilo, isopropilo, trifluoroetilo, ciclobutilo, ciclopentilo, difluorociclohexilo, metoxifenilo, tetrahidro-2H-tiopiran-4-ilo y tetrahidro-2H-piran-4-ilo;

R_1 es hidrógeno o metilo;

R_2 es metilo, trifluoroetilo, trifluorobutilo, pirimidinilo, trifluorometilpirimidinilo o ER_5;

R_3 es metilo, etilo, isopropilo, trifluorometilo, trifluoroetilo o ciclopropilo;

E es $-CH_2-$ o -C(O)-;

R_5 se selecciona del grupo que está constituido por ciclopentilo,

morfolinilo, fenilo, naftilo, benciloxi, pirimidinilo, piridinilo, quinolinilo, quinoxalinilo, pirazinilo, pirazolilo, bencimidazolilo, cinolinilo, naftidrinilo, pirido[2,3-b]pirazinilo, imidazo[4,5-c]piridinilo, benzotiadiazolilo, tetrahidropirazolo[1,5-a]piridinilo, dihidrobenzodioxinilo, imidazolilo, dihidrobenzofuranilo, triazolilo, oxazolilo, isoxazolilo, benzodioxinilo, tiazolilo, imidazo[1,2-a]piridinilo, tetrahidrobenzotiazolilo, dihidrobenzoxazinilo, tetrahidropiranilo, tetrahidropirazolo[1,5-a]azepinilo y dihidropirrolo[1,2-b]pirazolilo sustituido o sin sustituir.

3. El compuesto de la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, en el que:

R se selecciona del grupo que está constituido por isopropilo, ciclobutilo, ciclopentilo y tetrahidro-2H-piranilo;

R_1 es hidrógeno;

R_2 es ER_5;

R_3 es metilo o etilo;

E es $-CH_2-$; y

R_5 se selecciona del grupo que está constituido por fenilo, pirimidin-2-ilo, piridin-2-ilo, pirazin-2-ilo y 5-metilpirazin-2-ilo.

4. El compuesto de la reivindicación 1, seleccionado del grupo que está constituido por:

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-

1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-[(3S,4S)-4-metil-1-(4,5,6,7-tetrahidropirazolo[1,5-a]piridin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(1-metil-1H-bencimidazol-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(cinolin-3-ilmetil)-4-metilpirrolidin-3-il]-1-ciclopentil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-ciclopentil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona; y

1-ciclopentil-6-[(3S,4S)-1-{[2-(dimetilamino)pirimidin-4-il]metil}-4-metilpirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

o una sal farmacéuticamente aceptable del mismo.

5. El compuesto de la reivindicación 1, seleccionado del grupo que está constituido por:

6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-isopropil-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinoxalin-6-ilmetil)pirrolidin-3-il]-1,5-

dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S(4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(1,5-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(1,8-naftiridin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

1-isopropil-6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona; y

1-isopropil-6-[(3S,4S)-4-metil-1-(pirido[2,3-b]pirazin-8-ilmetil)pirrolidin-3-il]-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

o una sal farmacéuticamente aceptable del mismo.

6. El compuesto de la reivindicación 1, seleccionado del grupo que está constituido por:

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-

2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinolin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-4-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(6-metilpiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-{[6-(trifluorometil)piridin-3-il]metil}pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(1-metil-1H-imidazo[4,5-c]piridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(1,3-dimetil-1H-pirazol-5-il)metil]-4-metilpirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2,1,3-benzotiadiazol-5-ilmetil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinoxalin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(quinolin-4-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(3-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(35-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[4-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

3-metil-6-[(3S,4S)-4-metil-1-(piridin-3-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

3-metil-6-{(3S,4S)-4-metil-1-[(2-metilpirimidin-5-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-1-[(6-metoxipiridin-3-il)metil]-4-metilpirrolidin-3-il}-3-metil-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[(6-metilpiridin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(4-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-etilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2-fluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[2-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2,4-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(4-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-

4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-bencil-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-tiopiran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(2-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(3-metoxibencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-metil-1-[3-(trifluorometil)bencil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-1-(26-difluorobencil)-4-metilpirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-etil-1-[(5-metilpirazin-2-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-{(3S,4S)-4-etil-1-[(6-metoxipiridin-3-il)metil]pirrolidin-3-il}-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-etil-1-(piridin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-etil-1-(quinoxalin-2-ilcarbonil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

6-[(3S,4S)-4-metil-1-(pirimidin-2-ilmetil)pirrolidin-3-il]-1-(tetrahidro-2H-piran-4-il)-1,5-dihidro-4H-pirazolo[3,4-d]pirimidin-4-ona;

2-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo;

3-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo; y

4-({(3S,4S)-3-etil-4-[4-oxo-1-(tetrahidro-2H-piran-4-il)-4,5-dihidro-1H-pirazolo[3,4-d]pirimidin-6-il]pirrolidin-1-il}metil)benzonitrilo;

o una sal farmacéuticamente aceptable del mismo.

7. Una composición farmacéutica que comprende un compuesto de una cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable del mismo, y un vehículo, excipiente o diluyente farmacéuticamente aceptable.

8. La composición de la reivindicación 7, que comprende además un segundo agente farmacéutico.

9. La composición de la reivindicación 8, en la que el segundo agente farmacéutico se selecciona del grupo que está constituido por donepezilo, galantamina, memantina, rivastigmina y tacrina.

10. Un procedimiento para inhibir PDE9 en un mamífero en necesidad de tal inhibición que comprende la etapa de administrar al mamífero una cantidad inhibidora de PDE9 de un compuesto de una cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable del mismo.

11. Un procedimiento para tratar una enfermedad neurodegenerativa en un mamífero en necesidad de tal tratamiento, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de una cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable del mismo.

12. El procedimiento de la reivindicación 11, en el que la enfermedad es enfermedad de Alzheimer.

13.. Un procedimiento para promover la neurorrestauración en un mamífero en necesidad de tal neurorrestauración, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de una

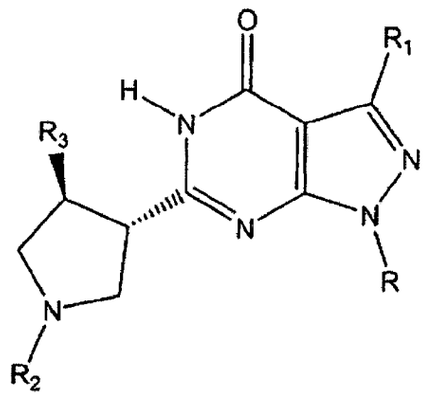
cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable del mismo.

14. Un procedimiento para mejorar deficiencias cognitivas en un mamífero en necesidad de tal mejora, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de un compuesto de una cualquiera de las reivindicaciones 1-6, o una sal farmacéuticamente aceptable del mismo.

15. El procedimiento de una cualquiera de las reivindicaciones 10-14 en el que el mamífero es humano.

RESUMEN

La invención proporciona compuestos inhibidores de PDE9 de fórmula (I),



(I)

y sales farmacéuticamente aceptables de los mismos, en la que R, R_1, R_2 y R_3 son como se definen en este documento. También se proporcionan composiciones farmacéuticas que contienen los compuestos de fórmula I y los usos de las mismas en el tratamiento de trastornos neurodegenerativos y cognitivos tales como enfermedad de Alzheimer y esquizofrenia.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

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PFIZER INC.
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150 East 42nd Street
New York NY 10017
ETATS-UNIS D'AMERIQUE

PFIZER INC.
SEP 2 2008
PATENT DEPARTMENT
LEGAL DIVISION - NYC

Date of mailing *(day/month/year)* 22/08/2008	
Applicant's or agent's file reference PC33468A	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IB2008/001125	International filing date *(day/month/year)* 05/05/2008
Applicant PFIZER INC.	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

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

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

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

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

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

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

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

4. **Reminders**

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

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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

DOCKETED
Due Date 10/22/08
SITE: NEW YORK

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

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

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

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

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

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

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

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

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

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

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
PC33468A		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2008/001125	05/05/2008	11/05/2007
Applicant		
PFIZER INC.		

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.

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

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

[X] 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. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. [ ] 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,**

[X] 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,**

[X] 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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/001125

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04

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)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FRANK WUNDER, ADRIAN TERSTEEGEN, ANNEGRET REBMANN, CHRISTINA ERB, THOMAS FAHRIG, AND MARTIN HENDRIX: "Characterization of the First Potent and Selective PDE9 Inhibitor Using a cGMP Reporter Cell Line" MOL PHARMACOL, vol. 68, no. 6, 2005, page 1775-1781, XP002491746 page 1777 -----	1-15

☐ 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 document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2008	22/08/2008

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

Form PCT/ISA/210 (second sheet) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2008/001125	05.05.2008	11.05.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04

Applicant
PFIZER INC.

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 usually 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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bader, Karl Günther Telephone No. +49 89 2399-7177

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2008/001125

Box No. I Basis of the 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. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. 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.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table 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.

5. Additional comments:

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)	Yes: Claims	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	1-15
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 Reference is made to the following document:

D1 : FRANK WUNDER, ADRIAN TERSTEEGEN, ANNEGRET REBMANN, CHRISTINA ERB, THOMAS FAHRIG, AND MARTIN HENDRIX: "Characterization of the First Potent and Selective PDE9 Inhibitor Using a cGMP Reporter Cell Line" MOL PHARMACOL, vol. 68, no. 6, 2005, page 1775-1781, XP002491746

Claims 10-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2 Document D1, which is considered to represent the most relevant state of the art, discloses (the references in parentheses applying to this document):
The first potent and selective PDE9 inhibitor with a pyrazolo-pyrimidine core.
From this, the subject-matter of independent claim 1 differs in that:
The compounds of formula I are of a particular stereochemistry and do invariably carry a pyrrolidine substituent on the pyrimidine.

2.1 The subject-matter of claim 1 is therefore novel (Article 33(2) PCT)
The problem to be solved by the present invention may be regarded as:
Provision of further PD9E inhibitors.

2.2 The solution to this problem proposed in claim 1 of the present application is considered as involving an inventive step (Article 33(3) PCT) for the following reasons:
The modifications necessary to arrive at the present subject matter claimed cannot be considered obvious in view of the skilled mans ability and the information available at the time of filing. Not even the features necessary to change/add to the D1 disclosure can be derived from the prior art in this context.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

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Characterization of the First Potent and Selective PDE9 Inhibitor Using a cGMP Reporter Cell Line

Frank Wunder, Adrian Tersteegen, Annegret Rebmann, Christina Erb, Thomas Fahrig, and Martin Hendrix

Cardiovascular Research (F.W., A.R.), Molecular Screening Technology (A.T.), CNS Research (C.E., T.F.), and Medicinal Chemistry (M.H.), Bayer HealthCare AG, Wuppertal, Germany

Received August 4, 2005; accepted September 8, 2005

ABSTRACT

We report here the in vitro characterization of 1-(2-chlorophenyl)-6-[(2*R*)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-one (BAY 73-6691), the first potent and selective inhibitor of phosphodiesterase 9 (PDE9), which is currently under preclinical development for the treatment of Alzheimer's disease. This compound selectively inhibits human (IC_{50} = 55 nM) and murine (IC_{50} = 100 nM) PDE9 activity in vitro and shows only moderate activity against other cyclic nucleotide-specific phosphodiesterases. We also report the generation and characterization of a stably transfected PDE9 Chinese hamster ovary cell line, additionally expressing soluble guanylate cyclase (sGC), the olfactory cyclic nucleotide-gated cation channel CNGA2 and the photoprotein aequorin. In this cell line, intracellular cGMP levels can be monitored in real-time via aequorin luminescence induced by Ca^{2+} influx through CNGA2, acting as the intracellular cGMP sensor. This simple and sensitive assay system was used for the characterization of the cellular activity of the new PDE9 inhibitor. BAY 73-6691 alone did not significantly increase basal cGMP levels in this experimental setting. However, in combination with submaximal stimulating concentrations of the sGC activator 4-[((4-carboxybutyl){2-[(4-phenethylbenzyl)oxy]phenethyl}amino)methyl] benzoic acid (BAY 58-2667), the compound induced concentration-dependent luminescence signals and intracellular cGMP accumulation. The PDE9 inhibitor significantly potentiated the cGMP signals generated by sGC activating compounds such as BAY 58-2667 or 5-cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-ylamine (BAY 41-2272) and induced leftward shifts of the corresponding concentration-response curves. Using our newly generated PDE9 reporter cell line, we could show that BAY 73-6691 is able to efficiently penetrate cells and to inhibit intracellular PDE9 activity.

Cyclic nucleotide-specific phosphodiesterases (PDEs) play an essential role in signal transduction by regulating the intracellular levels of cAMP and cGMP and, therefore, are important pharmacological targets. To date, 21 mammalian PDE genes have been identified and subgrouped into 11 isoenzyme families on the basis of their substrate specificity, regulation, and pharmacology (Beavo, 1995; Soderling and Beavo, 2000; Conti and Jin, 2001; Francis et al., 2001).

Phosphodiesterase 9 (PDE9) is a novel PDE family that has been identified and characterized recently. Only one member of this PDE family (PDE9A) is known so far. However, multiple alternatively spliced variants with differential tissue distribution and subcellular localization could be identified. High PDE9A expression was detected in various tissues, including brain, kidney, spleen, prostate, colon, and intestine. PDE9 is highly specific for cGMP and shows the highest affinity for cGMP of any PDE known to date (K_m = 0.07–0.17 μM). PDE9 is insensitive to a variety of known PDE inhibitors such as vinpocetine, EHNA, enoximone, rolipram, dipyridamole, and tadalafil, as well as the nonselective phosphodiesterase inhibitor 3-isobutyl-1-methyl-xanthine (IBMX). So far, no potent and selective PDE9 inhibitors are available. Only zaprinast (IC_{50} = 29–46 μM), sildenafil (IC_{50} = 2.6–11 μM), SCH 51866 (IC_{50} = 1.6–3.3 μM), and vard-

Article, publication date, and citation information can be found at http://molpharm.aspetjournals.org.
doi:10.1124/mol.105.017608.

ABBREVIATIONS: PDE, cyclic nucleotide-specific phosphodiesterase; CNG, cyclic nucleotide-gated; IBMX, 3-isobutyl-1-methylxanthin; sGC, soluble guanylate cyclase; RIA, radioimmunoassay; BSA, bovine serum albumin; CHO, Chinese hamster ovary; EHNA, *erythro*-9-(2-hydroxy-3-nonyl)adenine; BAY 73-6691, 1-(2-chlorophenyl)-6-[(2*R*)-3,3,3-trifluoro-2-methylpropyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-one; BAY 58-2667, 4-[((4-carboxybutyl){2-[(4-phenethyl-benzyl)oxy]phenethyl}amino)methyl] benzoic acid; BAY 41-2272, 5-cyclopropyl-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-4-ylamine; SCH 51866, *cis*-5,6a,7,8,9,9a-hexahydro-2-[4-(trifluoromethyl)phenylmethyl]-5-methylcyclopent[4,5]imidazo[2,1-*b*]purin-4(3*H*)-one; BAY 60-7550, 2-(3,4-dimethoxybenzyl)-7-[(1*R*)-1-[(1*R*)-1-hydroxyethyl]-4-phenylbutyl]-5-methylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one.

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enafil (IC_{50} = 0.58–3.4 μM) have been identified as weak and nonselective inhibitors of PDE9 (Fischer et al., 1998; Guipponi et al., 1998; Soderling et al., 1998; Corbin and Francis, 2002; Rentero et al., 2003; Wang et al., 2003; Bischoff, 2004).

In rodent brain, neuronal PDE9 expression has been detected in cerebellum, neocortex, caudate putamen, and hippocampus. According to the high expression of PDE9 in these brain regions, the enzyme might be involved in the regulation of neuronal cGMP levels and cGMP-mediated signal transduction (van Staveren et al., 2002). Several lines of evidence implicate a crucial involvement of cGMP in the process of learning and memory. Thus, it has been shown that activation of *N*-methyl-D-aspartate-type glutamate receptors on postsynaptic neurons activates NO synthase and stimulates the production of cGMP (Garthwaite, 1991). Blocking this activation through specific NO synthase inhibitors impairs memory performance in rodents (Yamada et al., 1996). On the other hand, it has been shown that intrahippocampal injection of the cGMP analog 8-bromo-cGMP improves learning (Bernabeu et al., 1996; Prickaerts et al., 2002). We have shown recently that blocking the degradation of cGMP with a specific inhibitor of PDE2 (which cleaves both cGMP and cAMP) results in enhanced memory performance in several rodent models of learning and memory (Boess et al., 2004). However, under physiological conditions, several PDEs are likely to simultaneously control cGMP levels in any given cell, possibly by affecting distinct subcellular cGMP pools.

Because the physiological role of PDE9 is not well-characterized, novel specific PDE9 inhibitors are highly desirable as both pharmacological tools and new potential therapeutics. We report here the in vitro characterization of BAY 73-6691, a novel potent and selective PDE9 inhibitor that currently is under preclinical development for the treatment of Alzheimer's disease (Hendrix, 2005).

To characterize the cellular activity of BAY 73-6691, we have generated a stably transfected PDE9 CHO cell line, additionally expressing soluble guanylate cyclase (sGC), the olfactory cyclic nucleotide-gated cation channel CNGA2, and the photoprotein aequorin. In this cGMP reporter cell line, intracellular cGMP levels can be monitored via aequorin luminescence induced by Ca^{2+} influx through CNGA2, acting as the intracellular cGMP sensor (Wunder et al., 2005).

We used the recombinant PDE9 cell line to identify and characterize the cellular effects of the selective PDE9 inhibitor BAY 73-6691 under basal and stimulated conditions. When combined with submaximal prestimulating concentrations of the soluble guanylate cyclase activator BAY 58-2667, BAY 73-6691 concentration-dependently induced luminescence signals and intracellular cGMP accumulation. BAY 73-6691 potentiated the aequorin luminescence and the cGMP levels generated by different soluble guanylate cyclase-activating compounds such as BAY 41-2272 and BAY 58-2667 (Stasch et al., 2001, 2002) and induced leftward shifts of the corresponding concentration-response curves.

Materials and Methods

Preparation of PDE Isoenzymes. Human PDEs and murine PDE9 [accession numbers NM_005020 (PDE1C), NM_002599 (PDE2A), NM_000922 (PDE3B), NM_002600 (PDE4B), NM_018945 (PDE7B), AF056490 (PDE8A), NM_002606 (PDE9A), AF031147 (mPDE9A), NM_006661 (PDE10A), and NM_016953 (PDE11A)] were recombinantly expressed in Sf9 insect cells using the pFASTBAC baculovirus expression system (Invitrogen, Carlsbad, CA). Cells were harvested and resuspended in lysis buffer (20 ml/1l cultures; 50 mM Tris-HCl, pH 7.4, 50 mM NaCl, 1 mM $MgCl_2$, 1.5 mM EDTA, and 10% glycerin). The cells were disrupted by sonication at 4°C, and cell debris was removed by centrifugation at 15,000*g* at 4°C for 30 min. The supernatant was designated PDE cell extract and was stored at −80°C. PDE5 was purified from human platelets by sonication followed by centrifugation and ion exchange chromatography of the supernatant on a Mono Q 10/10 column (linear NaCl gradient, elution with 0.2 to 0.3 M NaCl in buffer containing 20 mM HEPES, pH 7.2, and 2 mM $MgCl_2$).

Enzyme Inhibition. The commercially available [^{3}H]cAMP and [^{3}H]cGMP Scintillation Proximity Assay (GE Healthcare, Little Chalfont, Buckinghamshire, UK) system was used for enzyme inhibition studies. For the determination of the in vitro effect of test substances on the PDE reactions, 2 μl of the respective test compound in dimethyl sulfoxide (serial dilutions) were placed in wells of microtiter plates (Isoplate; PerkinElmer Wallac, Weiterstadt, Germany). Fifty milliliters of a dilution of PDE cell extract (see above) in buffer A (50 mM Tris-HCl, pH 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, and 0.2% BSA) was added. The dilution of the PDE cell extract was chosen such that the reaction kinetics were linear, and less than 70% of the substrate was consumed. The reaction was started by the addition of 50 μl (0.025 μCi) of 1:2000 in buffer A without BSA-diluted substrate, [8-^{3}H]guanosine 3′,5′-cyclic phosphate (PDE9 and PDE5), or [5′,8-^{3}H]adenosine 3′,5′-cyclic phosphate (all other PDEs) (1 μCi/μl; GE Healthcare). The PDE1 assay additionally contained 10^{-7} M calmodulin and 3 mM $CaCl_2$, and PDE2 was stimulated by the addition of 1 μM cGMP. After incubation at room temperature for 60 min, the reaction was stopped by the addition of 25 μl of a suspension containing 18 mg/ml yttrium scintillation proximity beads (GE Healthcare) in water. For PDE9, 25 μl of a PDE9 inhibitor dissolved in buffer A without BSA was added before the addition of beads (e.g., BAY 73-6691, 5 μM final concentration). The microtiter plates were measured in a Microbeta scintillation counter (PerkinElmer Wallac). IC_{50} values were determined from sigmoidal curves by plotting the percentage of PDE activity versus log compound concentration. IC_{50} is defined as the concentration of the inhibitor required to reduce the cyclic nucleotide hydrolyzing activity of tested PDEs by 50%.

Generation of the Recombinant PDE9 Cell Line. The cGMP reporter cell line, stably overexpressing soluble guanylate cyclase, was generated as described previously (Wunder et al., 2005). This cell line was cotransfected with the murine PDE9 cDNA (Soderling et al., 1998; mPDE9A1, accession number AF031147) in PCR3.1 and a plasmid providing hygromycin resistance (pCEP4d, EBNA-1 deletion). After selection with hygromycin, positive clones with high PDE9 expression and activity were identified by quantitative Taq-Man real-time reverse transcriptase-polymerase chain reaction (Applied Biosystems, Weiterstadt, Germany) and measurement of the PDE9 activity using the [^{3}H]cGMP scintillation proximity assay (GE Healthcare). Positive clones were further purified by the limited dilution technique. Plasmid vectors were purchased from Invitrogen.

Cell Culture Conditions and Luminescence Measurements. Cells were cultured at 37°C and 5% CO_2 in Dulbecco's modified Eagle's medium/Ham's F-12 medium (1:1) with L-glutamine, 15 mM HEPES, supplemented with 10% (v/v) inactivated fetal calf serum, 1 mM sodium pyruvate, 0.9 mM sodium bicarbonate, 50 U/ml penicillin, 50 μg/ml streptomycin, 2.5 μg/ml amphotericin B, 1 mg/ml geneticin, 0.25 mg/ml zeocin, and 0.6 mg/ml hygromycin. Next, 1800 cells/well were plated onto 384-well microtiter plates and cultured for 2 days. After removal of the cell-culture medium, cells were loaded for 3 h with 0.8 μg/ml coelenterazin in Ca^{2+}-free tyrode (130 mM NaCl, 5 mM KCl, 20 mM HEPES, 1 mM $MgCl_2$, and 4.8 mM $NaHCO_3$, pH 7.4) at 37°C and 5% CO_2. Compounds were added in Ca^{2+}-free tyrode for 6 min. IBMX (0.2 mM) was used in some exper-

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iments to prevent cGMP degradation by endogenous PDEs. Immediately after adding Ca^{2+} ions (final concentration, 3 mM), measurement of the aequorin luminescence was started by using a charge-coupled device camera (Hamamatsu Corporation, Shizuoka, Japan) in a light-tight box. Luminescence was monitored continuously for 40 s.

cGMP Determination by RIA. Cells were seeded on 24-well microtiter plates (20,000 cells/well) and cultured for 2 days. The medium was removed, the cells were washed once, and test compounds were added in Ca^{2+}-free tyrode for 10 min at 37°C. IBMX (0.2 mM) was used in some experiments to prevent cGMP degradation by endogenous PDEs. After removal of the supernatant, cGMP was extracted overnight with 70% EtOH at −20°C. Intracellular cGMP was measured by using a commercially available RIA kit (IBL, Hamburg, Germany). Measurements were performed in triplicate.

Compounds. BAY 73-6691 was synthesized by the chemistry department of Bayer HealthCare AG as described previously (Hendrix et al., 2004; example 37-2). BAY 58-2667 and BAY 41-2272 were synthesized as described previously (Alonso-Alija et al., 2001; Straub et al., 2001). EHNA, milrinone, trequinsin, and rolipram were purchased from Calbiochem (San Diego, CA). IBMX, dipyridamole, and vinpocetine were purchased from Sigma-Aldrich (Taufkirchen, Germany), and tadalafil was purified from commercially available tablets. BAY 60-7550 (Boess et al., 2004) was synthesized by the chemistry department of Bayer HealthCare AG.

Statistics. The data are presented as mean values with S.D. error. The GraphPad Prism Software (version 3.02; GraphPad Software Inc., San Diego, CA) was used for curve-fitting and calculation of the IC_{50} and EC_{50} values. The IC_{50} values were determined from three to six independent experiments. For the determination of EC_{50} values, three to four independent experiments were performed in quadruplicate. IC_{50} and EC_{50} values are given as means ± S.E.M.

Results

Potency and Selectivity of BAY 73-6691 against Different PDE Isoenzymes. In the search for novel PDE9 inhibitors, we could identify BAY 73-6691 (Fig. 1A), which potently inhibits human recombinant PDE9 with an IC_{50} value of 55 ± 9 nM as shown in Fig. 1B and a K_i value of 45 ± 15 nM (data not shown). The murine PDE9 is inhibited by BAY 73-6691 with an IC_{50} value of 100 ± 20 nM (Fig. 1B). We also studied the effects of BAY 73-6691 on different PDE isoenzymes, the corresponding IC_{50} values are shown in Table 1. BAY 73-6691 shows only moderate inhibition of human PDE1 (PDE1C; IC_{50} = 1400 ± 350 nM) and human PDE11 (IC_{50} = 2600 ± 400 nM) with selectivity ratios of 25 and 47, respectively. In addition, BAY 73-6691 shows very low potency against human PDE2, PDE3, PDE4, PDE5, PDE7, PDE8, and PDE10 (IC_{50} > 4000 nM).

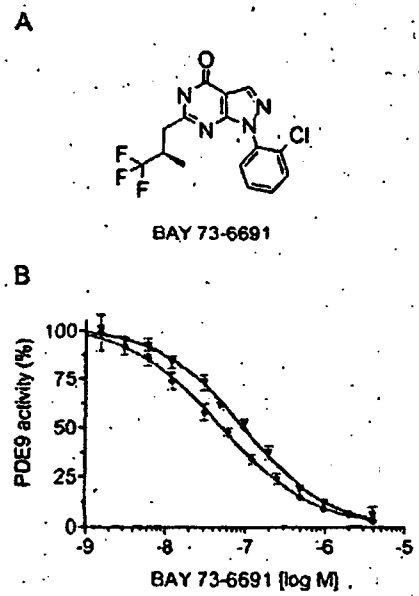


Fig. 1. BAY 73-6691 inhibits PDE9 activity in vitro. A, structure of BAY 73-6691. B, concentration-dependent inhibition of recombinant human (◆) and murine (▼) PDE9 by BAY 73-6691. Data are presented as mean values with S.D. error.

Generation of the Recombinant PDE9 Cell Line. A cGMP reporter cell line, stably overexpressing soluble guanylate cyclase, was generated as described previously (Wunder et al., 2005). This cell line was cotransfected with the murine PDE9 cDNA (Soderling et al., 1998; mPDE9A1) and a plasmid providing hygromycin resistance. After selection with hygromycin, positive clones with high PDE9 expression were identified by quantitative TaqMan real-time reverse transcriptase-polymerase chain reaction, and measurement of the PDE9 activity was performed after cell lysis by using the [^{3}H]cGMP Scintillation Proximity Assay (data not shown). Positive clones were further purified by the limited dilution technique, and one clonal PDE9 cell line was selected for further characterization. In this PDE9 cell line, intracellular cGMP accumulation can be monitored via Ca^{2+} influx and measurement of the aequorin luminescence (Wunder et al., 2005).

Characterization of the Cellular Activity of BAY 73-6691. We used the newly generated recombinant PDE9 cell line to characterize the cellular activity of BAY 73-6691. When applied to the cells under basal conditions without prestimulation, BAY 73-6691 did not induce significant luminescence signals (Fig. 2A) or intracellular cGMP accumulation measured by RIA (Fig. 4A). However, in combination with submaximal stimulating concentrations of the sGC activator BAY 58-2667 (Stasch et al., 2002), BAY 73-6691 induced concentration-dependent luminescence signals (Fig. 2A) and an increase of the intracellular cGMP concentration (Fig. 4A).

In the presence of 0.01, 0.03, and 0.1 μM BAY 58-2667,

TABLE 1

Selectivity profile of BAY 73–6691 against different human PDE isoenzymes

All enzymes were human recombinant, except for PDE5, which was purified from human platelets. IC_{50} values were determined from sigmoidal curves by plotting the percentage of PDE activity versus the log compound concentration. IC_{50} is defined as the concentration of the inhibitor (in nanomoles) required to reduce the cyclic nucleotide hydrolyzing activity of tested PDEs by 50%. The relative selectivity for PDE9A was determined by calculating the ratio between the IC_{50} for each PDE and the IC_{50} for PDE9.

	IC_{50}	Ratio
	nM	
PDE9A	55 ± 9	
PDE1C	1400 ± 350	25
PDE2A	≫4000	≫73
PDE3B	≫4000	≫73
PDE4B	≫4000	≫73
PDE5A	≫4000	≫73
PDE7B	≫4000	≫73
PDE8A	≫4000	≫73
PDE10A	≫4000	≫73
PDE11A	2600 ± 400	47

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BAY 73-6691 stimulated the aequorin luminescence with EC_{50} values of 28.2 ± 4.4, 4.3 ± 1.3, and 1.3 ± 0.1 μM, respectively. In combination with 0.1 μM BAY 58-2667, BAY 73-6691 significantly stimulated the aequorin luminescence with a minimum effective concentration of ~ 300 nM.

We also studied the effects of BAY 73-6691 in the absence of the nonselective phosphodiesterase inhibitor IBMX. Compared with the results obtained in the presence of IBMX (Fig. 3A), the concentration-dependent luminescence signals induced by the sGC activator BAY 58-2667 were diminished, and the corresponding concentration-response curve was shifted rightward (EC_{50} = 2.86 ± 0.86 μM; data not shown). Therefore, higher prestimulating concentrations of BAY 58-2667 were used. Under these conditions, BAY 73-6691 was able to induce concentration-dependent luminescence signals (Fig. 2B). In the presence of 0.03 μM, 0.1, and 1 μM BAY 58-2667, BAY 73-6691 stimulated the aequorin luminescence with EC_{50} values of 16.5 ± 2.3, 2.9 ± 0.4, and 1.4 ± 0.04 μM, respectively.

The effects of BAY 73-6691 on the parental cell line, which expresses soluble guanylate cyclase but lacks PDE9 expression, were also characterized. BAY 73-6691 induced only negligible luminescence signals and no significant intracellular cGMP accumulation in the parental cell line (Figs. 2C and 4B).

We also studied the effects of BAY 73-6691 on concentration-response curves of the sGC activating compounds BAY 58-2667 and BAY 41-2272 (Fig. 3). BAY 73-6691 was able to significantly enhance the luminescence signals (Fig. 3A) and the intracellular cGMP accumulation induced by BAY 58-2667 (Fig. 4C) and induced leftward shifts of the corresponding concentration-response curves. In the absence of BAY 73-6691, BAY 58-2667 stimulated the aequorin luminescence with an EC_{50} value of 373 ± 92 nM. In the presence of 0.1, 1, and 10 μM BAY 73-6691, the EC_{50} values were shifted to 296 ± 82, 198 ± 59, and 19.5 ± 4.0 nM, respectively. The EC_{50} value for intracellular cGMP accumulation induced by BAY 58-2667 in the absence of BAY 73-6691 was 340 ± 57 nM. In the presence of 1 and 10 μM BAY 73-6691, the EC_{50} values were reduced to 191 ± 49 and 30.8 ± 4.0 nM, respectively.

BAY 73-6691 also enhanced the luminescence signals stimulated by BAY 41-2272, a compound that stimulates cGMP

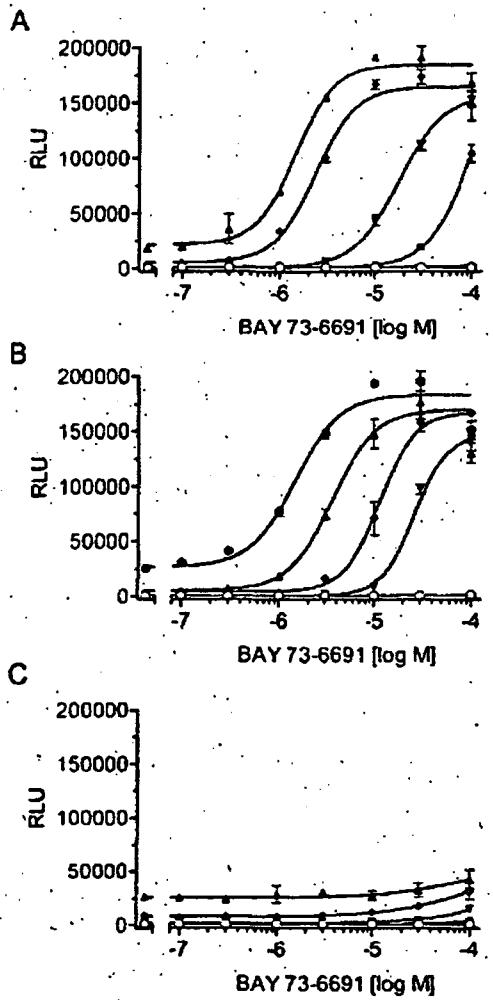


Fig. 2. Effects of the sGC activator BAY 58-2667 on BAY 73-6691 concentration-response curves. Stimulation of luminescence signals in the PDE9 cell line after 6-min incubation with BAY 73-6691 in Ca^{2+}-free tyrode with 0.2 mM IBMX (A) or without IBMX (B) in the absence (○) or presence of 0.003 μM (■), 0.01 μM (▼), 0.03 μM (◆), 0.1 μM (▲), and 1 μM (●) BAY 58-2667. C, stimulation of luminescence signals in the parental cell line expressing soluble guanylate cyclase but not PDE9 after 6-min incubation with BAY 73-6691 in Ca^{2+}-free tyrode with 0.2 mM IBMX in the absence or presence of BAY 58-2667 (0.003–0.1 μM). Measurements were started immediately after the addition of Ca^{2+}. Results are expressed as relative light units (RLU), and data are presented as mean values with S.D.

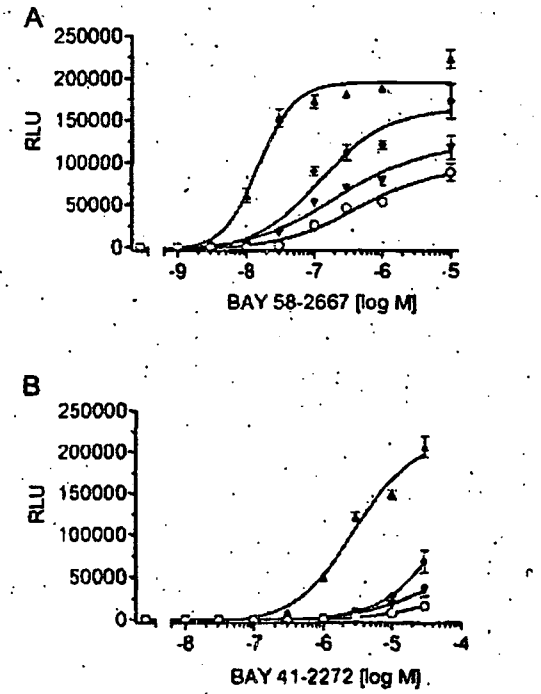


Fig. 3. Effects of the PDE9 inhibitor BAY 73-6691 on BAY 58-2667 and BAY 41-2272 concentration-response curves. Stimulation of luminescence signals in the PDE9 cell line after 6-min incubation with BAY 58-2667 (A) or BAY 41-2272 (B) in the absence (○) or presence of 0.1 μM (▼), 1 μM (◆), and 10 μM (▲) BAY 73-6691 in Ca^{2+}-free tyrode with 0.2 mM IBMX. Measurements were started immediately after the addition of Ca^{2+}. Data are presented as mean values with S.D.

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synthesis by sGC by a different mechanism from that of BAY 58-2667 (Stasch et al., 2001, 2002) and induced a leftward shift of the corresponding concentration-response curve (Fig. 3B). The minimum effective concentration of BAY 73-6691 that significantly potentiated BAY 58-2667 and BAY 41-2272 induced luminescence signals was 100 nM.

Activities of Other PDE Inhibitors on the PDE9 Reporter Cell Line. We also tested various PDE inhibitors in combination with submaximal stimulating concentrations of the sGC activator BAY 58-2667 for their ability to stimulate luminescence signal increases in the PDE9 reporter cell line. Vinpocetine, EHNA, BAY 60-7550 (PDE2 inhibitor; Boess et al., 2004), milrinone, trequinsin, rolipram, tadalafil, and dipyridamole were tested up to 100 μM and did not significantly enhance the aequorin luminescence (data not shown).

In contrast, the PDE5 inhibitors sildenafil and vardenafil, which have been reported to also weakly inhibit PDE9 (Soderling et al., 1998; Corbin and Francis, 2002; Bischoff, 2004), induced concentration-dependent luminescence signals in combination with submaximal prestimulating concentrations of BAY 58-2667 (Fig. 5).

Real-Time cGMP Measurements. To monitor changes of the intracellular cGMP levels induced by BAY 58-2667 in the absence or presence of IBMX and BAY 73-6691 in real time, compounds were added in tyrode containing 2 mM Ca^{2+} ions, and luminescence measurements were started immediately after the addition of compounds ("kinetic mode"; Wunder et al., 2005). The results are shown in Fig. 6. The addition of 0.3 μM BAY 58-2667 induced a weak luminescence signal that started after ~42 s. In the presence of IBMX, an increased luminescence signal, which already started after 36 s, was observed. Additional inhibition of PDE9 by 1 μM BAY 73-6691 further enhanced the luminescence signal and reduced the signal delay to 30 s.

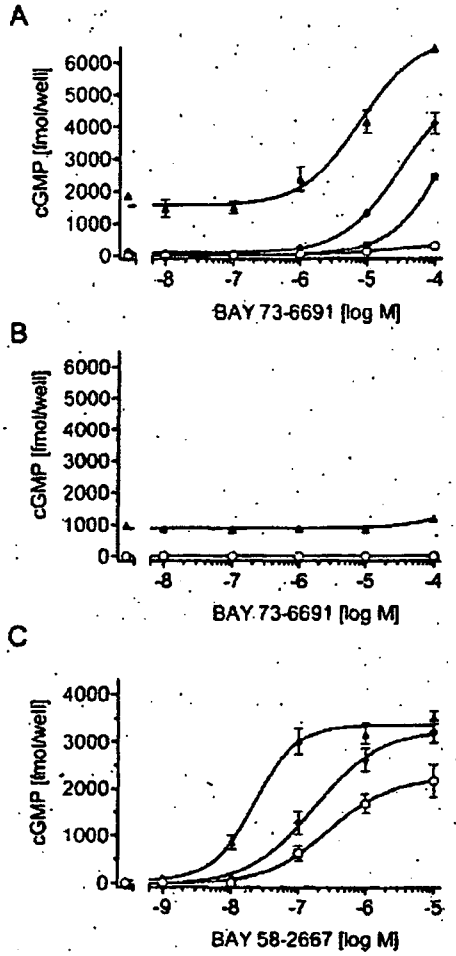


Fig. 4. Intracellular cGMP formation measured by RIA. A, concentration-dependent cGMP formation induced by BAY 73-6691 in the absence (○) or presence of 0.003 μM (■), 0.03 μM (◆), and 0.1 μM (▲) BAY 58-2667 in Ca^{2+}-free tyrode with 0.2 mM IBMX. B, effects of BAY 73-6691 on cGMP formation in the parental cell line expressing soluble guanylate cyclase but not PDE9 in the absence (○) or presence of 0.1 μM (▲) BAY 58-2667. Incubation in Ca^{2+}-free tyrode with 0.2 mM IBMX. C, stimulation of cGMP synthesis by BAY 58-2667 in the recombinant PDE9 cell line in the absence (○) or presence of 1 μM (●) and 10 μM (▲) BAY 73-6691 in Ca^{2+}-free tyrode with 0.2 mM IBMX. Data are presented as mean values with S.D.

Discussion

To date, 21 mammalian cyclic nucleotide-specific phosphodiesterases grouped into 11 isoenzyme families have been isolated and characterized leading to the development of selective inhibitors for several of the PDE families, most notably for PDE3, PDE4, and PDE5. These inhibitors are being evaluated as potential therapeutics for a variety of clinical indications. PDE9 represents a new family of cGMP-specific PDEs that was identified very recently. Therefore, no selective PDE9 inhibitors have been published so far. To elucidate the physiological relevance of this specific phospho-

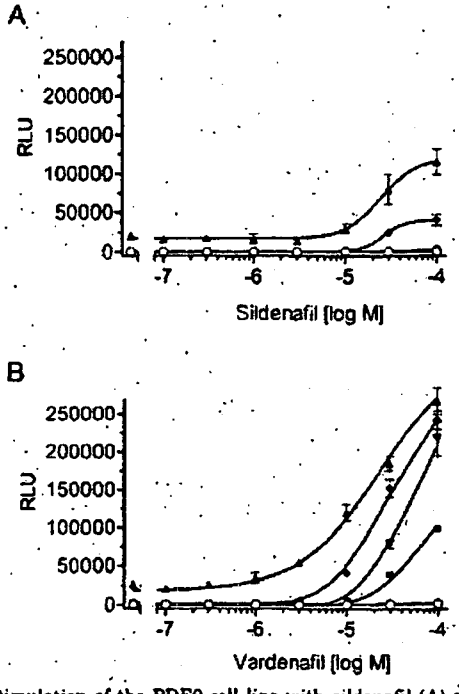


Fig. 5. Stimulation of the PDE9 cell line with sildenafil (A) and vardenafil (B) in the absence (○) or presence of 0.003 (■), 0.01 (▼), 0.03 (◆), and 0.1 μM (▲) BAY 58-2667. Cells were incubated for 6 min in Ca^{2+}-free tyrode with 0.2 mM IBMX. Measurements were started immediately after the addition of Ca^{2+}. Data are presented as mean values with S.D.

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diesterase, potent and selective PDE9 inhibitors are necessary and highly desirable.

We report here the identification of BAY 73-6691, the first potent and selective PDE9 inhibitor, currently under preclinical development for the treatment of Alzheimer's disease. BAY 73-6691 has been shown to improve long-term potentiation and was found to be active in several animal models of cognition (Hendrix, 2005).

In this study, we have characterized the activity of BAY 73-6691 in vitro. BAY 73-6691 selectively inhibits isolated human and murine PDE9 activity with submicromolar IC_{50} values. In addition, BAY 73-6691 shows only moderate inhibition of other PDE isoenzymes. The closest IC_{50} values were for PDE1 and PDE11, with selectivity ratios of 25 and 47, respectively. The other PDE isoenzymes were all minimally affected by BAY 73-6691, with IC_{50} values more than 100-fold higher than for PDE9.

A discrepancy between the in vitro activity on the isolated enzyme and the cellular activity has been reported for some PDE inhibitors (Pon et al., 1998; Marko et al., 2002). Therefore, it is highly desirable to have a simple and sensitive method for the characterization of the cellular activity of PDE inhibitors. Therefore, we have generated and characterized a recombinant PDE9 cell line. In this cGMP reporter cell line, intracellular cGMP synthesis can be stimulated by soluble guanylate cyclase activation. Intracellular cGMP accumulation leads to the activation of the cyclic nucleotide-gated cation channel CNGA2 and influx of Ca^{2+} ions. The Ca^{2+} influx can easily be monitored by aequorin luminescence measurements. This assay system is very sensitive for intracellular cGMP accumulation, and it has proven to be very robust (Wunder et al., 2005).

PDE9 is not inhibited, even at very high concentrations, by the nonselective phosphodiesterase inhibitor IBMX (Fischer et al., 1998; Soderling et al., 1998). Therefore, it is possible to specifically monitor PDE9 activity in the presence of IBMX, which inhibits other phosphodiesterases that are endogenously expressed in the CHO cell line. Hence, this newly generated reporter cell line is a powerful tool for the characterization of the cellular activity of PDE9 inhibitors.

Under nonstimulated conditions, BAY 73-6691 did not significantly increase basal cGMP levels or luminescence signals in the PDE9 cell line. However, in combination with submaximal stimulating concentrations of the sGC activator BAY 58-2667, BAY 73-6691 induced concentration-dependent luminescence signals and intracellular cGMP accumulation. With increasing concentrations of BAY 58-2667, the BAY 73-6691-stimulated luminescence signals also increased. An optimal prestimulation of the cGMP synthesis was observed at ~0.03 μM BAY 58-2667. Under these conditions, a maximal stimulation of the aequorin luminescence of approximately 100-fold could be induced by the addition of BAY 73-6691. Higher concentrations of BAY 58-2667 stimulated significant luminescence signals even in the absence of BAY 73-6691, and a diminished signal-to-background ratio was observed.

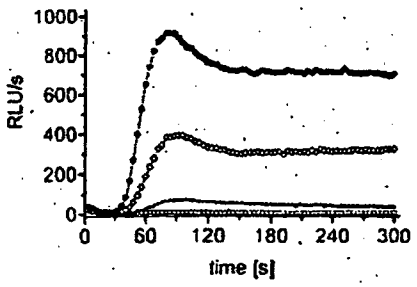


Fig. 6. Real-time detection of intracellular cGMP accumulation. Kinetics of the luminescence signals generated by 0.3 μM BAY 58-2667 in the presence of Ca^{2+} ions ("kinetic mode"): control (○), BAY 58-2667 (▲), BAY 58-2667 with 0.2 mM IBMX (◇), and BAY 58-2667 with 0.2 mM IBMX and 1 μM BAY 73-6691 (●).

When the same set of experiments was repeated in the absence of the nonselective PDE inhibitor IBMX, approximately 3- to 10-fold higher concentrations of BAY 58-2667 were necessary to induce a comparable level of prestimulation compared with the experiments performed in the presence of IBMX. However, the luminescence signals induced by BAY 73-6691 in combination with BAY 58-2667 reached similar maximum levels, and the corresponding concentration-response curves were shifted rightward. This might be caused by the presence of endogenously expressed phosphodiesterases which are involved in cGMP turnover in these cells and are sensitive to inhibition by IBMX.

Recombinant expression of PDE9 in the cGMP reporter cell line reduced the ability of the sGC activator BAY 58-2667 to stimulate intracellular cGMP accumulation. In the parental cell line, BAY 58-2667 stimulated the aequorin luminescence with an EC_{50} value of 10.3 ± 1.7 nM (Wunder et al., 2005). In the recombinant PDE9 cell line, this EC_{50} value was shifted to 373 ± 92 nM in the absence of BAY 73-6691, which points to a high recombinant expression level and activity of PDE9 within this cell line. The addition of 10 μM BAY 73-6691 significantly enhanced the luminescence signals induced by BAY 58-2667 and reduced the EC_{50} value to 19.5 ± 4.0 nM. These results imply that the PDE9 inhibitor BAY 73-6691 is able to inhibit most of the intracellular PDE9 activity at a concentration of 10 μM, which is in good agreement with the inhibition curve using the isolated enzyme. Thus, BAY 73-6691 is able to efficiently penetrate cells and to inhibit the intracellular PDE9 activity.

In the parental CHO cell line, BAY 73-6691 did not significantly potentiate luminescence signals or intracellular cGMP accumulation induced by BAY 58-2667. These results imply that the endogenous expression of PDE9 in the CHO cell line is very low. In contrast, in the recombinant PDE9 cell line, BAY 73-6691 significantly potentiated the luminescence signals induced by different types of soluble guanylate cyclase activators, as exemplified here with BAY 58-2667 and BAY 41-2272, and induced leftward shifts of the corresponding concentration-response curves. These results were further confirmed by RIA measurements of the intracellular cGMP accumulation induced by BAY 58-2667 in the presence or absence of BAY 73-6691, which correlated very well with the luminescence measurements.

Depending on the particular experimental design, the minimum effective concentration of BAY 73-6691 that significantly enhanced the aequorin luminescence signals was in the range of 100 to 300 nM. Although the intracellular concentration of BAY 73-6691 is not known, these extracellular concentrations are comparable with or only slightly higher than the IC_{50} value of 100 nM for inhibition of the murine PDE9 in vitro, which suggests that the drug is rapidly and efficiently taken up by the cells.

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The PDE5 inhibitors sildenafil and vardenafil have been reported as weak inhibitors of PDE9 (Corbin and Francis, 2002; Bischoff, 2004). As expected, both compounds stimulated concentration-dependent luminescence signals in our newly generated PDE9 cell line which could only be detected in the presence of submaximal stimulating concentrations of the sGC activator BAY 58-2667. The rank order of potency for the stimulation of luminescence signals by these two PDE5 inhibitors compared with BAY 73-6691 fits very well to their respective IC_{50} values for PDE9 inhibition in vitro: BAY 73-6691 > vardenafil >. sildenafil. The activity of sildenafil and vardenafil on the PDE9 cell line could not be ascribed to PDE5 inhibition because tadalafil, a potent PDE5 inhibitor that does not inhibit PDE9 (Corbin and Francis, 2002), shows no activity in this experimental setting. We also tested several additional phosphodiesterase inhibitors that where also found to be inactive on our PDE9 cell line. Therefore, PDE9 activity and inhibition can be selectively monitored using this PDE9 reporter cell line.

We also determined the kinetics of cGMP accumulation induced by BAY 58-2667 in the absence or presence of the nonselective phosphodiesterase inhibitor IBMX and the PDE9 inhibitor BAY 73-6691. In the absence of any PDE inhibitor, BAY 58-2667 apparently stimulated only minor intracellular cGMP accumulation and, therefore, induced only small increases in the observed luminescence signal. Subsequent addition of IBMX and BAY 73-6691 significantly increased the luminescence signals induced by BAY 58-2667 and reduced the signal delay as well as the time to peak. It is interesting that the addition of 1 μM BAY 73-6691, a concentration which does not fully inhibit PDE9, on top of IBMX more than doubled the observed luminescence signal, indicating that the intracellular PDE9 activity is very high.

Because intracellular PDE9 inhibition and cGMP accumulation can easily be monitored by aequorin luminescence measurements, the PDE9 reporter cell line is suitable for the search of new PDE9 inhibitors by ultra-high-throughput screening. In a similar approach, the parental cell line was used in an automated ultra-high-throughput screening assay, which ultimately led to the successful identification of a new class of soluble guanylate cyclase activators (Stasch et al., 2002; Wunder et al., 2005).

In summary, we have identified the first potent and selective PDE9 inhibitor, BAY 73-6691. Using our newly generated PDE9 reporter cell line, we show that BAY 73-6691 is able to efficiently penetrate cells and to inhibit intracellular PDE9 activity. Thereby, BAY 73-6691 is able to significantly amplify the cGMP responses elicited by stimulators of the nitric oxide/cGMP pathway.

Acknowledgments

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCIÓN [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que 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 [ ]

ESQUEMA DE TRAZADO [ ]

- 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 [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 10-11-2009

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2020

Doctor(a)
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Apoderado(a) y/o Representante de
PFIZER INC.

REFERENCIA	Radicación No.	9 127785
	Solicitud internacional	PCT/IB2008/001125
	Fecha inicio fase nacional	11/12/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	384

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)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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.

Continua en la página siguiente...

Radicación No.:9 127785

JESUS FERNEL GARCIA GARCIA
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 15 ENE. 2019
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