Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-53380

54. **TÍTULO** ANTAGONISTA DEL RECEPTOR DE PEPTIDO RELACIONADO CON EL GEN DE CALCITONINA

51. **CLASIFICACIÓN INTERNACIONAL** A61P 25/06 A61K 31/535

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

PETITORIO

AS: 101.199

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radi: 06-053380- -00000-0000
Fec: 2006-06-02 16:22:40 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYM
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 1024

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and Province Line Road, Princeton, New Jersey 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	Nombre: Andrew P. Degnan, Ling Chen, Rita Civiello, Gene M. Dubowchik, Xiaojun Han, Xiang Jun J. Jiang, John E. Macor, George Tora, Guanglin Luo Dirección: 123 York Street, Apt. 22-P, New Haven, CT 06511, US; 193 McCormick Lane, Middletown, CT 06457, US; 90 Cow Hill Road, Killingworth, CT 06419, US; 65 Spring Street, Middlefield, CT 06455, US; 65 Ridgecrest Drive, Cheshire, CT 06410, US; 760 Mix Ave., #2L, Hamden, CT 06514, US; 644 Mosse Hill Road, Guilford, CT 06437, US; 30 N. Meadow Lane, Meriden, CT 06450, US; 135 Devonshire Lane, Madison, CT 06443, Estados Unidos de América (Respectivamente) Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

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Solicitud Internacional No. PCT/US2003/038799 Fecha 05-12-2003
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Título (54): ANTAGONISTA DEL RECEPTOR DE PEPTIDO RELACIONADO CON EL GEN DE CALCITONINA

7 Clasificación Internacional (51) _____

8 Prioridad SI ☐ NO ☒	(33) País de Origen	(32) Fecha	(31) Número de Solicitud

9 Comprobante de pago No. 06-40,583 **Fecha** 01-06-20065

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

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $463.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. **Fotocopia autenticada**
- [ ] 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 efectuado por la IPEA.
- [ ] Traducción del examen preliminar 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 12x12.
- [ ] 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.
- [x] Otros: Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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FECHA : MAYO 30 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
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***** 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	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/US2003/038799 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES BRISTOL – MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO ANTAGONISTA DEL RECEPTOR DE PEPTIDO RELACIONADO CON EL GEN DE CALCITONINA

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) ANDREW P. DuGNAN, LING CHEN, RITA CIVIELLO, GENE M. DUBOWCHIK, XIAOJUN HAN,

OTROS XIANG JUN J. JIANG, JOHN E. MACOR, GEORGE TORA, GUANGLIN LUO

OFICINA DE COMUNICACIONES

PCT/US2003/038799

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

MAKUJINA, Shah
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

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BMS PATENT LAW
SEP 07 2005
Docketed Item
Due Date
Attorney SRM

Date of mailing (day/month/year)	
20 September 2005 (20.09.2005)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
10135PCT	
International application No.	**International filing date (day/month/year)**
PCT/US2003/038799	05 December 2003 (05.12.2003)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
		US 22 Sep 2005
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

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

☒ the person ☒ the name ☒ the address ☒ the nationality ☒ the residence

Name and Address	State of Nationality	State of Residence
LUO, Guanglin 135 Devonshire Lane Madison, CT 06443 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant/inventor for the United States of America only.

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

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Rodolfo CLEMENTE
Facsimile No. +41 22 338 7090	Telephone No. (41-22) 338 8458

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(71) Applicant *(for all designated States except US)*: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US). CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US). CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US). DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US). HAN, Xiaojun [CN/US]; 65 Ridgecrest Drive, Cheshire, CT 06410 (US). JIANG, Xiang, Jun, J. [US/US]; 760 Mix Ave., #2L, Hamden, CT 06514 (US). MACOR, John, E. [US/US]; 644 Mossc Hill Road, Guilford, CT 06437 (US). TORA, George [KR/US]; 30 N. Meadow Lane, Meriden, CT 06450 (US).

(74) Agents: MAKUJINA, Shah et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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

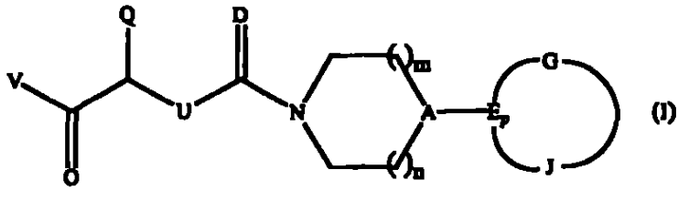
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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/065779 A1

(54) Title: CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I) as antagonists of calcitonin gene-related peptide receptors ("CGRP-receptor"), pharmaceutical compositions comprising them, methods for identifying them, methods of treatment using them and their use in therapy for treatment of neurogonic vasodilation, neurogenic inflammation, migraine and other headaches, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.

CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS

Field of the Invention

The present invention relates to novel small molecule antagonists of calcitonin gene-related peptide receptors ("CGRP-receptor"), pharmaceutical compositions comprising them, methods for identifying them, methods of treatment using them and their use in therapy for treatment of neurogenic vasodilation, neurogenic inflammation, migraine, cluster headache and other headaches, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.

Background of the Invention

Calcitonin gene-related peptide (CGRP) is a naturally occurring 37-amino-acid peptide first identified in 1982 (Amara, S. G. et al, *Science* 1982, *298*, 240-244). Two forms of the peptide are expressed (αCGRP and βCGRP) which differ by one and three amino acids in rats and humans, respectively. The peptide is widely distributed in both the peripheral (PNS) and central nervous system (CNS), principally localized in sensory afferent and central neurons, and displays a number of biological effects, including vasodilation.

When released from the cell, CGRP binds to specific cell surface G protein-coupled receptors and exerts its biological action predominantly by activation of intracellular adenylate cyclase (Poyner, D. R. et al, *Br J Pharmacol* 1992, *105*, 441-7; Van Valen, F. et al, *Neurosci Lett* 1990, *119*, 195-8.). Two classes of CGRP receptors, $CGRP_1$ and $CGRP_2$, have been proposed based on the antagonist properties of the peptide fragment CGRP(8–37) and the ability of linear analogues of CGRP to activate $CGRP_2$ receptors (Juaneda, C. et al. *TiPS* 2000, *21*, 432-438). However, there is lack of molecular evidence for the $CGRP_2$ receptor (Brain, S. D. et al, *TiPS* 2002, *23*, 51-53). The $CGRP_1$ receptor has three components: (i) a 7 transmembrane calcitonin receptor-like receptor (CRLR); (ii) the single transmembrane receptor activity modifying protein type one (RAMP1); and (iii) the intracellular receptor component protein (RCP) (Evans B. N. et al., *J Biol Chem.* 2000, *275*, 31438-43).

RAMP1 is required for transport of CRLR to the plasma membrane and for ligand binding to the CGRP-receptor (McLatchie, L. M. et al, *Nature* 1998, *393*, 333-339). RCP is required for signal transduction (Evans B. N. et al., *J Biol Chem.* 2000, *275*, 31438-43). There are known species-specific differences in binding of small molecule antagonists to the CGRP-receptor with typically greater affinity seen for antagonism of the human receptor than for other species (Brain, S. D. et al, *TiPS* 2002, *23*, 51-53). The amino acid sequence of RAMP1 determines the species selectivity, in particular, the amino acid residue Trp74 is responsible for the phenotype of the human receptor (Mallee et al. *J Biol Chem* 2002, *277*, 14294-8).

Inhibitors at the receptor level to CGRP are postulated to be useful in pathophysiologic conditions where excessive CGRP receptor activation has occurred. Some of these include neurogenic vasodilation, neurogenic inflammation, migraine, cluster headache and other headaches, thermal injury, circulatory shock, menopausal flushing, and asthma. CGRP receptor activation has been implicated in the pathogenesis of migraine headache (Edvinsson L. *CNS Drugs* 2001;15(10):745-53; Williamson, D. J. *Microsc. Res. Tech.* 2001, *53*, 167-178.; Grant, A. D. *Brit. J. Pharmacol.* 2002, *135*, 356-362.). Serum levels of CGRP are elevated during migraine (Goadsby PJ, et al. *Ann Neurol* 1990;28:183-7) and treatment with anti-migraine drugs returns CGRP levels to normal coincident with alleviation of headache (Gallai V. et al. *Cephalalgia* 1995;15: 384-90). Migraineurs exhibit elevated basal CGRP levels compared to controls (Ashina M, et al., Pain. 2000;86(1-2):133-8.2000). Intravenous CGRP infusion produces lasting headache in migraineurs (Lassen LH, et al. *Cephalalgia*. 2002 Feb;22(1):54-61). Preclinical studies in dog and rat report that systemic CGRP blockade with the peptide antagonist CGRP(8-37) does not alter resting systemic hemodynamics nor regional blood flow (Shen, Y-T. et al, *J Pharmacol Exp Ther* 2001, *298*, 551-8). Thus, CGRP-receptor antagonists may present a novel treatment for migraine that avoids the cardiovascular liabilities of active vasoconstriction associated with non-selective 5-$HT_{1B/1D}$ agonists, 'triptans' (e.g., sumatriptan).

There are various *in vivo* migraine models known in the literature (see De Vries, P. et al, *Eur J Pharmacol* 1999, *375*, 61-74). Some electrically stimulate the trigeminal ganglion and measure dilation of the intracranial vessels which they innervate (e.g., Williamson et al. *Cephalalgia* 1997 17:518-24). Since facial arteries

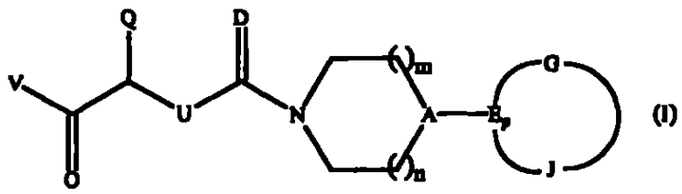
are also innervated by the trigeminal nerve, other models study changes in facial blood flow induced by electrical trigeminal activation (e.g., Escott et al. *Brain Res* 1995 669:93). Alternatively, other peripheral nerves (e.g., saphenous) and vascular beds (e.g., abdominal blood flow) are also studied (e.g., Escott et al. *Br J Pharmacol* 1993 *110*, 772-6;). All models have been shown to be blocked by pretreatment with the peptide antagonist CGPR(8-37) a peptide fragment that is absent the 1st seven residues, or by a small molecule CGRP-receptor antagonist. In some instances, exogenous CGRP has been used as a stimulus. However, these models are all invasive terminal procedures, and none have shown the clinically important abortive effect of reversing an established increase in artery dilation or increased blood flow using post-treatment of a CGRP-receptor antagonist. Williamson et al. Cephalalgia 1997 17:518-24, and Williamson et al. Cephalalgia. 1997 17:525-31: used *inter alia* i.v. CGRP as a stimulus to increase intracranial dural artery diameter in sodium pentobarb anesthetized rats employing a terminal 'intravital' procedure that involved drilling to thin the skull and the creation of a closed cranial window to visualize dural arteries. The effect was blocked by pretreatment with i.v. CGRP(8-37). Escott et al. Brain Res 1995 669:93; *inter alia* drilled into the rat skull and used brain electrodes to electrically stimulate the trigeminal ganglion and measured laser Doppler facial blood flow in a terminal procedure in sodium pentobarb anesthetized rats involving neuromuscular blockade, tracheal intubation and artificial ventilation. The effect was blocked by pretreatment with CGRP(8-37). Escott et al. *Br J Pharmacol* 1993 *110*, 772-6; *inter alia* used intradermal (i.d.) CGRP as the stimulus to increase blood flow in rat abdominal skin of sodium pentobarb anesthetized animals outfitted with cannulated jugular veins for anesthetic and drug delivery. The effect was blocked by pretreatment with i.v. CGRP(8-37). Chu et al. *Neurosci Lett* 2001 *310*, 169-72 used *inter alia* i.d. CGRP as the stimulus in rats and measured laser Doppler changes in blood flow in the skin of the back in a terminal method using sodium pentobarb anesthetized and tracheal cannulated animals; and showed pretreatment blockade by continuous release of CGRP(8-37) from subcutaneously (s.c.) implanted osmotic pumps. Hall et al *Br J Pharmacol* 1995 *114*, 592-7 and Hall et al *Br J Pharmacol* 1999 *126*, 280-4 *inter alia* used topical CGRP to increase hamster cheek pouch arteriole diameter, and i.d. CGRP to increase blood flow in rat dorsal skin of sodium pentobarb anesthetized animals outfitted with cannulated jugular veins for anesthetic

and drug delivery. The effect was blocked by pretreatment with i.v. CGRP(8-37). Doods et al. Br J Pharmacol. 2000 Feb;129(3):420-3 *inter alia* drilled into the skull of the marmoset (new world monkey) and used brain electrodes to produce electrical stimulation of the trigeminal ganglion and measured facial blood flow in an invasive terminal procedure involving neuromuscular blockade and artificial ventilation of sodium pentobarbital anesthetized primates. Increase in flow was blocked by pre-treatment of a small molecule CGRP antagonist. *See also* WO 03/272252 Isolated DNA Molecules Encoding Humanized Calcitonin Gene-Related Peptide Receptor, Related Non-Human Transgenic Animals and Assay Methods. Thus the method of the present invention procedure being *inter alia* a non-invasive survival model in primates measuring exogenous CGRP-induced changes in facial blood flow and demonstrating pre- and post-treatment effects of peptide and small molecule CGRP antagonists in spontaneously breathing isoflurane anesthetized marmosets who recover from the procedure offers significant advantages.

A number of non-peptidic, small molecule CGRP-receptor antagonists have been recently reported. WO 97/09046 and equivalents disclose *inter alia* quinine and quinidine related compounds which are ligands, in particular antagonists, of CGRP-receptor. WO 98/09630 and WO 98/56779 and equivalents disclose *inter alia* variously substituted, nitrobenzamide compounds as CGRP-receptor antagonists. WO 01/32649, WO 01/49676, and WO 01/32648 and equivalents disclose *inter alia* a series of 4-oxobutanamides and related cyclopropane derivatives as CGRP-receptor antagonists. WO 00/18764, WO 98/11128 and WO 00/55154 and equivalents disclose *inter alia* benzimidazolinyl piperidines as antagonists to CGRP-receptor. Unrelated to CGRP, a series of somatostatin antagonists have been disclosed in WO 99/52875 and WO 01/25228 and equivalents. *See also* U.S. 6,344,449, U.S. 6,313,097, U.S. 6,521,609, U.S. 6,552,043, US 20030181462, US20030191068 and WO 03/076432 and related applications. Thus, novel CGRP-receptor antagonists effective for the treatment of neurogenic inflammation, migraine and other disorders would be greatly advantageous.

Summary of the Invention

Thus according to a first embodiment of the first aspect of the present invention are provided compounds of Formula (I)



(I)

and pharmaceutically acceptable salts and solvates thereof

wherein

V is $-N(R^1)(R^2)$ or OR^4;

R^4 is H, C_{1-6}alkyl, C_{1-4}haloalkyl or $(C_{1-4}alkylene)_{0-1}R^{4'}$

$R^{4'}$ is C_{3-7}cycloalkyl, phenyl, adamantyl, quinuclidyl, azabicyclo[2.2.1]heptyl, azetidinyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino or dioxolanyl; and

$R^{4'}$ is optionally substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, hydroxy, amino, C_{3-7}cycloalkyl, C_{1-3}alkylamino, C_{1-3}dialkylamino, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl; and

$R^{4'}$ optionally contains 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the ring structure of $R^{4'}$;

R^1 and R^2 are each independently L^1, wherein L^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $-C_{1-6}alkylene\text{-}amino(C_{1-3}alkyl)_2$, C_{3-7}cycloalkyl, phenyl, azetidinyl, adamantyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl,

pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino and dioxolanyl; and

R^1 and R^2 are each optionally and independently substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, hydroxy, amino, C_{3-7}cycloalkyl, C_{1-3}alkylamino, C_{1-3}dialkylamino, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl;

R^1 and R^2 optionally and independently contain 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the heterocycles comprising R^1 and R^2;

wherein L^1 is optionally and independently interrupted from the nitrogen to which it is attached by L^2, wherein L^2 is independently C_{1-3}alkylene or C_{1-3}alkylidene; or

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino;

wherein X is optionally substituted with Y, wherein Y is dioxolanyl, C_{1-9}alkyl, C_{2-9}alkenyl, C_{2-9}alkynyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkoxy, C_{3-7}cycloalkyl, phenyl, azetidinyl, furanyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazolidinonyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, pyridyl, pyrimidinyl, dihydrobenzimidazolonyl, piperazinyl,

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piperidinyl, morpholino, benzothiazolyl, benzisothiazolyl or thiomorpholino;

and wherein X and Y are

optionally interrupted with Z, wherein Z is –NHC(O)O-, –NHC(O)NH-, $NC(O)NH_2$, -NH-, $-C_{1-3}$alkylene-, $-C_{1-3}$alkylene-, $-C_{1-3}$alkenylene-NHC(O)O-C_{1-3}alkylene-; and

optionally and independently substituted with 1 or 2 of the same or different substituents selected from the group consisting of C_{1-4}alkyl, amino, C_{1-3}alkylamino, $-C_{1-6}$alkylene-amino$(C_{1-3}alkyl)_2$, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl;

X and Y optionally and independently contain 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the heterocycles comprising X and Y;

provided that if X is substituted with Y, and if X and Y are not interrupted with Z, then X and Y optionally share one carbon atom and together form a spirocyclic moiety;

Q is Q' or Q";

wherein

Q' is $(S^y)_nR^3$; and

Q" is $NH(S^y)_nR^3$, $NHC(O)(S^y)_nR^3$, $NHC(O)O(S^y)_nR^3$, $NHC(O)NH(S^y)_nR^3$, $O(S^y)_nR^3$, $(S^y)_nNHR^3$,

$(S^y)_sNHC(O)R^3$, $(S^y)_sNHC(O)OR^3$, $(S^y)_sNHC(O)NHR^3$ or $(S^y)_sOR^3$;

wherein S^y is C_{1-3}alkylene or C_{1-3}alkylidene and s is 0 or 1;

U is CH_2 or NH;

provided that if Q is Q^n, then U is CH_2;

R^3 is R^{3a} or R^{3b}

wherein

R^{3a} is

(i) a heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to five of the same or different heteroatoms selected from the group consisting of O, N and S and said heterocycle optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused rings;

(ii) a 4 to 6 membered heterocycle containing one to three of the same or different heteroatoms selected from the group consisting of O, N and S, optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle;

(iii) C_{3-7}cycloalkyl;

(iv) carbazolyl, fluorenyl, phenyl, -O-phenyl, -O-C_{1-4}alklylene-phenyl, or napthyl; or

(v) C_{1-8}alkyl, C_{2-7}alkenyl, $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, $-C(O)O-R^{3'}$ or C_{2-7}alkynyl; and

wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C_{1-3}alkylenephenyl, -C_{1-3}alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C_{1-6}alkyl, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, $(C_{1-3}alkyl)_{1-2}$amine,

$-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ and $-SO_2R^{3'}$;

$R^{3'}$ is H or $-C_{1-6}$alkyl;

provided that if R^{3a} is , $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ or $-C(O)O-R^{3'}$, then said $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ or $-C(O)O-R^{3'}$ are unsubstituted;

R^{3b} is R^{3a} but is not phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-1-naphthyl, 1H-indol-3-yl, 1-methyl-1H-indol-3-yl, 1-formyl-1H-indol-3-yl, 1-(1,1-dimethylethoxycarbonyl)-1H-indol-3-yl, 4-imidazolyl, 1-methyl-4-imidazolyl, 2-thienyl, 3-thienyl, thiazolyl, 1H-indazol-3-yl, 1-methyl-1H-indazol-3-yl, benzo[b]fur-3-yl, benzo[b]thien-3-yl, pyridinyl, quinolinyl or isoquinolinyl; optionally substituted in the carbon skeleton with mono-, di- or trisubstituted by fluorine, chlorine or bromine atoms or by branched or unbranched alkyl groups, C_{3-8} -cycloalkyl groups, phenylalkyl groups, alkenyl, alkoxy, phenyl, phenylalkoxy, trifluoromethyl, alkoxycarbonylalkyl, carboxyalkyl, alkoxycarbonyl, carboxy, dialkylaminoalkyl, dialkylaminoalkoxy, hydroxy, nitro, amino, acetylamino, propionylamino, benzoyl, benzoylamino, benzoylmethylamino, methylsulphonyloxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkanoyl, cyano, tetrazolyl, phenyl, pyridinyl, thiazolyl, furyl, trifluoromethoxy, trifluoromethylthio, trifluoromethylsulphinyl- or trifluoromethylsulphonyl groups;

wherein said substituents may be the same or different and the above-mentioned benzoyl, benzoylamino- and benzoylmethylamino groups may in turn additionally be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom, or by an alkyl, trifluoromethyl, amino or acetylamino group;

D is O, NCN or NSO_2C_{1-3}alkyl;

A is C, N or CH;

m and n are independently 0, 1 or 2;

provided that

if m and n are 0, then A is not N;

if m is 2, then n is not 2; or

if n is 2, then m is not 2;

E is N, CH or C;

p is 0 or 1;

if p is 1, then G, J and E together form A^x or A^y;

A^x is a fused heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to four of the same or different heteroatoms selected from the group consisting of O, N and S; and

optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused heterocycle;

A^y is a 4 to 6 membered heterocycle containing one to three heteroatoms selected from the group consisting of O, N and S; and

optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle;

wherein A^x and A^y are optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, cyano, C_3-

7cycloalkyl, phenyl, halophenyl, halo, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; or

if p is 0 such that G and J are each attached to A, then A is C, and G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA' or GJA";

wherein

GJA' is A^x or A^y; and

GJA" is A^x or A^y;

provided that

A^x is not a 1,3-diaza-fused heterocycle; and

A^y is not a 1,3-diaza-heterocycle;

and further provided that

if Q is Q", then R^3 is R^{3a}; and

if Q is Q', then

R^3 is R^{3b}; or

R^3 is R^{3a}, p is 0 and G, J and A together form GJA".

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and R^3 is R^{3b}.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', R^3 is R^{3a} and p is 0 such that G, J and A together form GJA".

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and Q' is $(S^y)_sR^3$ and s is 0.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and Q' is $(S^y)_sR^3$, S^y is C_{1-3}alkylene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and Q' is $(S^y)_sR^3$, S^y is C_{1-3}alkylidene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and U is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', Q' is $(S^y)_s R^3$, s is 0 and U is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', Q' is $(S^y)_s R^3$, S^y is C_{1-3}alkylene, s is 1and U is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', Q' is $(S^y)_s R^3$, S^y is C_{1-3}alkylidene, s is 1and U is CH_2.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and U is NH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', Q' is $(S^y)_s R^3$, s is 0 and U is NH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q', Q' is $(S^y)_s R^3$, S^y is C_{1-3}alkylene, s is 1and U is NH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the

present invention wherein Q is Q', Q' is $(S^y)_s R^3$, S^y is C_{1-3}alkylidene, s is 1and U is NH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q".

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NH(S^y)_sR^3$.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NH(S^y)_sR^3$ and s is 0.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NH(S^y)_sR^3$, S^y is C_{1-3}alkylene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NH(S^y)_sR^3$, S^y is C_{1-3}alkylidene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)(S^y)_sR^3$.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)(S^y)_sR^3$ and s is 0.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)(S^y)_sR^3$, S^y is C_{1-3}alkylene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)(S^y)_sR^3$, S^y is C_{1-3}alkylidene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)O(S^y)_sR^3$.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)O(S^y)_sR^3$ and s is 0.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)O(S^y)_sR^3$, S^y is C_{1-3}alkylene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)O(S^y)_sR^3$, S^y is C_{1-3}alkylidene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)NH(S^y)_sR^3$.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)NH(S^y)_sR^3$ and s is 0.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)NH(S^y)_sR^3$, S^y is C_{1-3}alkylene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and Q" is $NHC(O)NH(S^y)_sR^3$, S^y is C_{1-3}alkylidene and s is 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is OR^4.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is OR^4 and R^4 is C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is $-N(R^1)(R^2)$.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein

V is $-N(R^1)(R^2)$ or OR^4;

R^4 is H, C_{1-6}alkyl, C_{1-4}haloalkyl, $(C_{1-4}$alkylene$)_{0-1}R^{4'}$

$R^{4'}$ is C_{3-7}cycloalkyl, phenyl, adamantyl, quinuclidyl, azabicyclo[2.2.1]heptyl, azetidinyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino or dioxolanyl; and

$R^{4'}$ is optionally substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, hydroxy, amino, C_{3-7}cycloalkyl, C_{1-3}alkylamino, C_{1-3}dialkylamino, $(C_{1-3}$alkyl$)_{0-2}$ureido, phenyl and benzyl;

$R^{4'}$ optionally contains 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the ring structure of $R^{4'}$;

R^1 and R^2 are each independently L^1, wherein L^1 is selected from the group consisting of H, C_{1-6}alkyl, $-C_{1-6}$alkylene-amino$(C_{1-3}$alkyl$)_2$, C_{3-7}cycloalkyl, phenyl, adamantyl, azetidinyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl,

imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino and dioxolanyl; and

R^1 and R^2 are each optionally and independently substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, hydroxy, amino, C_{3-7}cycloalkyl, C_{1-3}alkylamino, C_{1-3}dialkylamino, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl;

R^1 and R^2 optionally and independently contain 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the heterocycles comprising R^1 and R^2;

wherein L^1 is optionally interrupted from the nitrogen to which it is attached by L^2, wherein L^2 is C_{1-3}alkylene; or

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is azetidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino;

wherein X is optionally substituted with Y, wherein Y is dioxolanyl, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkoxy, C_{3-7}cycloalkyl, phenyl, azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazolidinonyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, pyridyl, pyrimidinyl, dihydrobenzimidazolonyl, piperazinyl,

piperidinyl, morpholino, benzothiazolyl, benzisothiazolyl or thiomorpholino;

and wherein X and Y are

optionally interrupted with Z, wherein Z is –NHC(O)O-, –NHC(O)NH-, NC(O)NH_2, -NH-, -C_{1-3}alkylene-, -C_{1-3}alkylene-NHC(O)O-C_{1-3}alkylene-; and

optionally and independently substituted with 1 or 2 of the same or different substituents selected from the group consisting of C_{1-4}alkyl, amino, C_{1-3}alkylamino, -C_{1-6}alkylene-amino$(C_{1-3}alkyl)_2$, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl;

X and Y optionally and independently contain 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of the heterocycles comprising X and Y;

provided that if X is substituted with Y, and if X and Y are not interrupted with Z, then X and Y optionally share one carbon atom and together form a spirocyclic moiety.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^4 is H, C_{1-6}alkyl, C_{1-4}haloalkyl or $(C_{1-4}alkylene)_{0-1}R^{4'}$; $R^{4'}$ is C_{3-7}cycloalkyl, phenyl, adamantyl, quinuclidyl, azabicyclo[2.2.1]heptyl, azetidinyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl,

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is azetidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, piperazinyl, piperidinyl, morpholino or thiomorpholino;

wherein X is substituted with Y, wherein Y is dioxolanyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, phenyl, azetidinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrrolidinonyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazolidinonyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, azepinyl, diazepinyl, pyridyl, pyrimidinyl, dihydrobenzimidazolonyl, piperazinyl, piperidinyl, morpholino, benzothiazolyl, benzisothiazolyl or thiomorpholino;

and wherein X and Y optionally share one carbon atom and together form a spirocyclic moiety.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is $-N(R^1)(R^2)$ and

R^1 and R^2 are each independently L^1, wherein L^1 is selected from the group consisting of H, C_{1-4}alkyl, or

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is piperidinyl or morpholino;

wherein X is substituted with Y, wherein Y is dioxolanyl, C_{1-4}alkyl or piperidinyl;

and wherein X and Y optionally share one carbon atom and together form a spirocyclic moiety.

triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino or dioxolanyl; and $R^{4'}$ is optionally substituted with 1 or 2 of the same or different substituents selected from the group consisting of halo, cyano, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{1-4}alkoxy, hydroxy, amino, C_{3-7}cycloalkyl, C_{1-3}alkylamino, C_{1-3}dialkylamino, $(C_{1-3}alkyl)_{0-2}$ureido, phenyl and benzyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^4 is H, C_{1-6}alkyl, C_{1-4}haloalkyl or $(C_{1-4}alkylene)_{0-1}R^{4'}$; $R^{4'}$ is C_{3-7}cycloalkyl, phenyl, adamantyl, quinuclidyl, azabicyclo[2.2.1]heptyl, azetidinyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino or dioxolanyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^4 is H, C_{1-6}alkyl or $(C_{1-4}alkylene)_{0-1}R^{4'}$; $R^{4'}$ is C_{3-7}cycloalkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is $-N(R^1)(R^2)$ and

R^1 and R^2 are each independently L^1, wherein L^1 is selected from the group consisting of H, C_{1-6}alkyl, $-C_{1-6}$alkylene-amino$(C_{1-3}alkyl)_2$, C_{3-7}cycloalkyl, phenyl, azetidinyl, adamantyl, tetrahydrofuranyl, furanyl, dioxolanyl, thienyl, tetrahydrothienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, pyranyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, piperidinyl, piperazinyl, morpholino, thiomorpholino and dioxolanyl; or

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According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is -N(R^1)(R^2) and wherein R^1 and R^2 are each independently L^1, wherein L^1 is selected from the group consisting of H, C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is -N(R^1)(R^2) and wherein

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is piperidinyl or morpholino;

wherein X is substituted with Y, wherein Y is

dioxolanyl, C_{1-4}alkyl or piperidinyl;

and wherein X and Y optionally share one carbon atom and together form a spirocyclic moiety.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is -N(R^1)(R^2) and wherein

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is piperidinyl;

wherein X is substituted with Y, wherein Y is

piperidinyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is -N(R^1)(R^2) and wherein

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is morpholino;

wherein X is substituted with Y, wherein Y is C_{1-4}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is -N(R^1)(R^2) and wherein

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is piperidinyl;

wherein X is substituted with Y, wherein Y is C_{1-4}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein V is $-N(R^1)(R^2)$ and wherein

R^1 and R^2 together with the nitrogen to which they are attached form X,

wherein X is piperidinyl;

wherein X is substituted with Y, wherein Y is dioxolanyl;

and wherein X and Y share one carbon atom and together form a spirocyclic moiety.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein X and Y are not interrupted with Z.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein X and Y are not interrupted with Z; and X and Y share one carbon atom and together form a spirocyclic moiety

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a}.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b}.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is a heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to five of the same or different heteroatoms selected from the group consisting of O, N and S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is a heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to five of the same or different heteroatoms selected from the group consisting of O, N and S and said heterocycle optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused rings.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is a heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to five of the same or different heteroatoms selected from the group consisting of O, N and S and said heterocycle optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused rings; wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C_{1-3}alkylphenyl, -C_{1-3}alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, C_{1-6}alkoxy, $(C_{1-3}alkyl)_{1-2}$amine, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ and $-SO_2R^{3'}$; $R^{3'}$ is H or -C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is a 4 to 6 membered heterocycle containing one to three of the same or different heteroatoms selected from the group consisting of O, N and S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is a 4 to 6 membered heterocycle containing one to three of the same or different heteroatoms selected from the group consisting of O, N and S, optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the

present invention wherein R^{3a} is a 4 to 6 membered heterocycle containing one to three of the same or different heteroatoms selected from the group consisting of O, N and S, optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle; wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C_{1-3}alkylphenyl, -C_{1-3}alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, C_{1-6}alkoxy, $(C_{1-3}alkyl)_{1-2}$amine, -$OR^{3'}$, -$C(O)R^{3'}$, -$C(O)O$-$R^{3'}$, -O-$C(O)R^{3'}$, -$N(R^{3'})_2$, -$C(O)N(R^{3'})_2$, -$N(R^{3'})C(O)(R^{3'})_2$, -$N(R^{3'})C(O)N(R^{3'})_2$, -$N(R^{3'})C(O)OR^{3'}$, -O-$C(O)N(R^{3'})_2$, -$N(R^{3'})SO_2R^{3'}$, -$SO_2N(R^{3'})_2$ and -$SO_2R^{3'}$; $R^{3'}$ is H or -C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is C_{3-7}cycloalkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is C_{3-7}cycloalkyl; wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C_{1-3}alkylphenyl, -C_{1-3}alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, C_{1-6}alkoxy, $(C_{1-3}alkyl)_{1-2}$amine, -$OR^{3'}$, -$C(O)R^{3'}$, -$C(O)O$-$R^{3'}$, -O-$C(O)R^{3'}$, -$N(R^{3'})_2$, -$C(O)N(R^{3'})_2$, -$N(R^{3'})C(O)(R^{3'})_2$, -$N(R^{3'})C(O)N(R^{3'})_2$, -$N(R^{3'})C(O)OR^{3'}$, -O-$C(O)N(R^{3'})_2$, -$N(R^{3'})SO_2R^{3'}$, -$SO_2N(R^{3'})_2$ and -$SO_2R^{3'}$; $R^{3'}$ is H or -C_{1-6}alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is carbazolyl, fluorenyl, phenyl, -O-phenyl, -O-C_{1-4}alklylene-phenyl, or napthyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is carbazolyl, fluorenyl, phenyl, -O-phenyl, -O-C_{1-4}alklylene-phenyl, or napthyl; wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, -O-C_{1-3}alkylphenyl, -C_{1-3}alkylene-OC(O)-phenyl, cyano, amino, nitro,

halo, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, C_{1-6}alkoxy, $(C_{1-3}alkyl)_{1-2}$amine, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ and $-SO_2R^{3'}$; $R^{3'}$ is H or $-C_{1-6}$alkyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is C_{1-8}alkyl, C_{2-7}alkenyl, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ or C_{2-7}alkynyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^{3a} is C_{1-8}alkyl, C_{2-7}alkenyl, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ or C_{2-7}alkynyl; wherein R^{3a} is optionally substituted with 1 to 3 of the same or different substituents selected from the group consisting of benzyl, phenyl, -O-phenyl, $-O-C_{1-3}$alkylphenyl, $-C_{1-3}$alkylene-OC(O)-phenyl, cyano, amino, nitro, halo, C_{1-3}mono-bi-tri-haloalkyl, C_{1-3}mono-bi-tri-haloalkyloxy, C_{1-6}alkoxy, $(C_{1-3}alkyl)_{1-2}$amine, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ and $-SO_2R^{3'}$; $R^{3'}$ is H or $-C_{1-6}$alkyl; provided that if R^{3a} is $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ or $-C(O)O-R^{3'}$, then said $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ or $-C(O)O-R^{3'}$ are unsubstituted.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is phenyl, hydroxyphenyl, azetidinyl, napthyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynl, dihydroquinolinonyl, hydroquinolinonyl, quinolinyl, dihydroisoquinolinonyl, hydroisoquinolinonyl, isoquinolinyl, dihydroquinazolinonyl, hydroquinazolinonyl, quinazolinyl, dihydroquinoxalinonyl, hydroquinoxalinonyl, quinoxalinyl, benzimidazolyl, indazolyl, dihydrobenzimidazolonyl, hydrobenzimidazolonyl, benzimidazolinyl, dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzoxazolyl, benzotriazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, benzothienyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, benzofuranyl, benzdioxolanyl, dihydroindolonyl, hydroindolonyl, indolyl, indolizinyl, isoindolyl, indolinyl, indazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, furanyl, thienyl, pyrrolyl, pyrrolinyl,

pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, purinyl, carbazolyl, pyrimidinyl, piperidinyl, triazolopyrimidinyl, tetrahydropyrazolopyridinyl, piperazinyl or morpholino; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is phenyl, napthyl, indazolyl, benzimidazolinyl, dihydrobenzoxazolyl, benzotriazolyl, benzothienyl, benzdioxolanyl, dihydroindolonyl, indolyl, furanyl, thienyl, pyridyl, purinyl, carbazolyl, piperidinyl, triazolopyrimidinyl, tetrahydropyrazolopyridinyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, benzothienyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, benzofuranyl, dihydroindolonyl, hydroindolonyl, indolyl, indolizinyl, isoindolyl, indolinyl or indazolyl; optionally substituted as provided in the first embodiment of the first aspect.

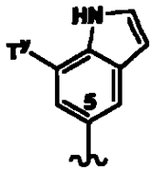
According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is dihydrobenzoxazolyl, benzotriazolyl, indolyl, halonitrophenyl, halopyrimidine, halopurinyl, C_{1-3}alkyl-nitroaminopyrimidine, triazolopyrimidinyl, pyridyl, indazolyl, phenyl or benzdioxolanyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3a} and R^{3a} is naphthyl, phenyl-O-phenyl, or thienyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b}.

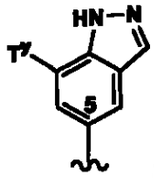
According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} and R^{3b} is

1H-Indol-5-yl



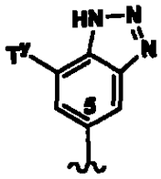
;

1H-Indazol-5-yl



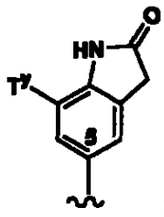
;

1H-Benzotriazol-5-yl



;

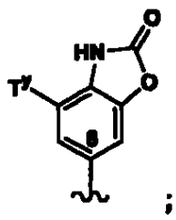
1,3-Dihydro-indol-2-on-5-yl



;

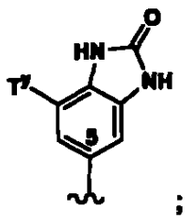
3H-Benzooxazol-2-on-6-yl

34



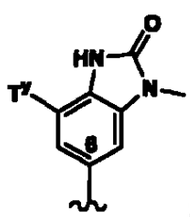
;

1,3-Dihydro-benzoimidazol-2-on-5-yl



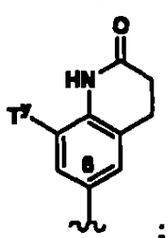
;

1-Methyl-1,3-dihydro-benzoimidazol-2-on-6-yl



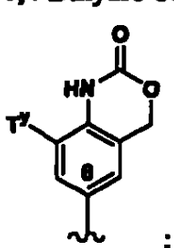
;

3,4-Dihydro-1H-quinolin-2-on-6-yl



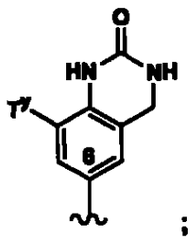
;

1,4-Dihydro-benzo[d][1,3]oxazin-2-on-6-yl



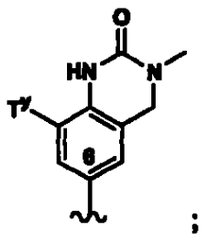
;

3,4-Dihydro-1H-quinazolin-2-on-6-yl



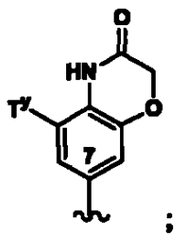
;

3-Methyl-3,4-dihydro-1H-quinazolin-2-on-6-yl



; or

4H-Benzo[1,4]oxazin-3-on-7-yl



;

wherein T^y is H, C_{1-4}alkyl, F, Cl, Br or nitrile.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} and R^{3b} is azetidinyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynl, dihydroquinolinonyl, hydroquinolinonyl, dihydroisoquinolinonyl, hydroisoquinolinonyl, dihydroquinazolinonyl, hydroquinazolinonyl, quinazolinyl, dihydroquinoxalinonyl, hydroquinoxalinonyl, quinoxalinyl, benzimidazolyl, 1H-indazol-5-yl, dihydrobenzimidazolonyl, hydrobenzimidazolonyl, benzimidazolinyl, dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, benzdioxolanyl, dihydrobenzoxazolyl, benzotriazolyl, dihydroindolonyl, hydroindolonyl, indolizinyl, isoindolyl, indolinyl, pyrazolyl,

pyrazolinyl, pyrazolidinyl, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, purinyl, carbazolyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 isR^{3b} and R^{3b} is dihydrobenzimidazolonyl, hydrobenzimidazolonyl, benzimidazolinyl, dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, 1H-indazol-5-yl, benzdioxolanyl, dihydrobenzoxazolyl, benzotriazolyl, dihydroindolonyl, hydroindolonyl, indolizinyl, isoindolyl, indolinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, purinyl, carbazolyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 isR^{3b} and R^{3b} is azetidinyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynl, dihydroquinolinonyl, hydroquinolinonyl, dihydroisoquinolinonyl, hydroisoquinolinonyl, dihydroquinazolinonyl, hydroquinazolinonyl, quinazolinyl, dihydroquinoxalinonyl, hydroquinoxalinonyl, quinoxalinyl, benzimidazolyl, 1H-indazol-5-yl, dihydrobenzimidazolonyl, hydrobenzimidazolonyl, benzimidazolinyl, dihydro-benzthiazolonyl, hydrobenzthiazolonyl, benzthiazolyl, dihydrobenzothiophenonyl, hydrobenzothiophenonyl, dihydrobenzofuranonyl, hydrobenzofuranonyl, benzdioxolanyl, dihydrobenzoxazolyl, benzotriazolyl, purinyl, carbazolyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 isR^{3b} and R^{3b} is azetidinyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynl, dihydroquinolinonyl, hydroquinolinonyl, dihydroisoquinolinonyl, hydroisoquinolinonyl, dihydroquinazolinonyl, hydroquinazolinonyl, quinazolinyl,

dihydroquinoxalinonyl, hydroquinoxalinonyl, quinoxalinyl, benzimidazolyl, benzdioxolanyl, dihydrobenzoxazolyl, benzotriazolyl, dihydroindolonyl, hydroindolonyl, 1H-indazol-5-yl, indolizinyl, isoindolyl, indolinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, purinyl, carbazolyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} and R^{3b} is benzdioxolanyl, dihydrobenzoxazolyl, benzotriazolyl, purinyl, carbazolyl; optionally substituted as provided in the first embodiment of the first aspect.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein R^3 is R^{3b} and R^{3b} is dihydrobenzoxazolyl, benzotriazolyl, indolyl, halonitrophenyl, halopyrimidinyl, halopurinyl, C_{1-3}alkyl-nitroaminopyrimidinyl, triazolopyrimidinyl, pyridyl, 1H-indazol-5-yl, phenyl or benzdioxolanyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and wherein said compounds have an absolute configuration of R.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q' and wherein said compounds have an absolute configuration of S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein Q is Q" and wherein said compounds have an absolute configuration of R.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the

present invention wherein Q is Q" and wherein said compounds have an absolute configuration of S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein m and n are each 1.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein D is O.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A is C.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A is CH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A is N.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein E is N.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein E is CH.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein E is C.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein said compounds exhibit as described herein a CGRP Binding IC_{50} of less than 10 nM.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the

present invention wherein said compounds exhibit as described herein a CGRP Binding IC_{50} of less than 100 nM.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein said compounds exhibit as described herein a CGRP Binding IC_{50} of less than 1000 nM.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 1; and G, J and E together form A^x or A^y.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 1; and G, J and E together form A^x.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 1; and G, J and E together form A^y.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^x is a fused heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to four of the same or different heteroatoms selected from the group consisting of O, N and S; and optionally containing 1 or 2 carbonyls wherein the carbon atom of said carbonyl is a member of said fused heterocycle.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^x is a fused heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to four of the same or different heteroatoms selected from the group consisting of O, N and S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^x is a fused heterocycle having two fused rings with 5 to 7 members in each of said rings, said heterocycle containing one to four of the same or different heteroatoms selected from the group consisting of O, N and S and wherein A^x is substituted with phenyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^x is a fused heterocycle described herein.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^y is a 4 to 6 membered heterocycle containing one to three heteroatoms selected from the group consisting of O, N and S; and optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^y is a 4 to 6 membered heterocycle containing one to three heteroatoms selected from the group consisting of O, N and S.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^y is a 4 to 6 membered heterocycle containing one to three heteroatoms selected from the group consisting of O, N and S; and optionally containing 1 to 2 carbonyls, wherein the carbon atom of said carbonyl is a member of said 4 to 6 membered heterocycle; and wherein A^y is substituted with phenyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein A^y is a 4 to 6 membered heterocycle described herein.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA' or GJA".

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA'.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA".

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA' and GJA' is A^x.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA' and GJA' is A^y.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA" and GJA" is A^x.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are GJA" and GJA" is A^y.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydroquinoxalinonyl, dihydrobenzoxazinyl, hydrobenzoxazinyl, dihydrobenzoxazinonyl,

dihydrobenzimidazolonyl, dihydrobenzimidazolyl, dihydro-benzthiazolonyl, dihydrobenzthiazolyl, dihydrobenzothiophenonyl, dihydrobenzofuranonyl, dihydroindolonyl, indolinyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholino; wherein said heterocycle is optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, cyano, C_{3-7}cycloalkyl, phenyl, halophenyl, furanyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydroquinoxalinonyl, dihydrobenzoxazinyl, hydrobenzoxazinyl, dihydrobenzoxazinonyl, dihydrobenzimidazolonyl, dihydrobenzimidazolyl, dihydro-benzthiazolonyl, dihydrobenzthiazolyl, dihydrobenzothiophenonyl, dihydrobenzofuranonyl, dihydroindolonyl, indolinyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholino; wherein said heterocycle is optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, cyano, C_{3-7}cycloalkyl, phenyl, halophenyl, furanyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, piperidinyl, piperazinyl or morpholino.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydrobenzofuranonyl, dihydroindolonyl, indolinyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholino; wherein said

heterocycle is optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, cyano, C_{3-7}cycloalkyl, phenyl, halophenyl, piperazinyl or morpholino.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydroquinoxalinonyl, dihydrobenzoxazinyl, hydrobenzoxazinyl, dihydrobenzoxazinonyl, dihydrobenzimidazolonyl, dihydrobenzimidazolyl, dihydro-benzthiazolonyl, dihydrobenzthiazolyl, dihydrobenzothiophenonyl, dihydrobenzofuranonyl, dihydroindolonyl, indolinyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl and morpholino.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydroquinoxalinonyl, dihydrobenzoxazinyl, hydrobenzoxazinyl and dihydrobenzoxazinonyl.

According to another embodiment of the first aspect of the present invention are provided compounds according to the first embodiment of the first aspect of the present invention wherein p is 0 such that G and J are each attached to A, then G, J and A together form a spirocyclic ring system with said rings of said system containing A and wherein G, J and A together are form a heterocycle selected from the group consisting of imidazolinonyl, imidazolidinonyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydroquinazolinonyl, dihydroquinoxalinonyl and dihydrobenzoxazinyl.

According to various embodiments of a second aspect of the present invention are provided pharmaceutical compositions comprising compounds of Formula (I) as defined herein.

According to various embodiments of a third aspect of the present invention are provided methods of treating inflammation (particularly neurogenic inflammation), headache (particularly migraine), pain, thermal injury, circulatory shock, diabetes, Reynaud's syndrome, peripheral arterial insufficiency, subarachnoid/ cranial hemorrhage, tumor growth, flushing associated with menopause and other conditions the treatment of which can be effected by the antagonism of the CGRP receptor by the administration of pharmaceutical compositions comprising compounds of Formula (I) as defined herein.

According to various embodiments of a fourth aspect of the present invention are uses of the compounds of the present invention selected from the group consisting of (a) immune regulation in gut mucosa (b) protective effect against cardiac anaphylactic injury (c) stimulating or preventing interleukin-1b(IL-1b)-stimulation of bone resorption (d) modulating expression of NK1 receptors in spinal neurons and (e) airway inflammatory diseases and chronic obstructive pulmonary disease including asthma. *See (a)* Calcitonin Receptor-Like Receptor Is Expressed on Gastrointestinal Immune Cells. Hagner, Stefanie; Knauer, Jens; Haberberger, Rainer; Goeke, Burkhard; Voigt, Karlheinz; McGregor, Gerard Patrick. Institute of Physiology, Philipps University, Marburg, Germany. Digestion (2002), 66(4), 197-203; *(b)* Protective effects of calcitonin gene-related peptide-mediated evodiamine on guinea-pig cardiac anaphylaxis. Rang, Wei-Qing; Du, Yan-Hua; Hu, Chang-Ping; Ye, Feng; Tan, Gui-Shan; Deng, Han-Wu; Li, Yuan-Jian. School of Pharmaceutical Sciences, Department of Pharmacology, Central South University, Xiang-Ya Road 88, Changsha, Hunan, Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 367(3), 306-311; *(c)* The experimental study on the effect calcitonin gene-related peptide on bone resorption mediated by interleukin-1. Lian, Kai; Du, Jingyuan; Rao, Zhenyu; Luo, Huaican. Department of Orthopedics, Xiehe Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Peop. Rep. China. Journal of Tongji Medical University (2001), 21(4), 304-307, *(d)* Calcitonin gene-related Peptide regulates expression of neurokinin1 receptors by rat spinal neurons. Seybold VS, McCarson KE, Mermelstein PG, Groth RD, Abrahams LG. J. Neurosci. 2003 23 (5): 1816-1824. epartment of Neuroscience, University of Minnesota, Minneapolis, Minnesota 55455, and Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City,

Kansas 66160 *(e)* Attenuation of antigen-induced airway hyperresponsiveness in CGRP-deficient mice. Aoki-Nagase, Tomoko; Nagase, Takahide; Oh-Hashi, Yoshio; Shindo, Takayuki; Kurihara, Yukiko; Yamaguchi, Yasuhiro; Yamamoto, Hiroshi; Tomita, Tetsuji; Ohga, Eijiro; Nagai, Ryozo; Kurihara, Hiroki; Ouchi, Yasuyoshi. Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan. American Journal of Physiology (2002), 283(5,Pt. 1), L963-L970; *(f)* Calcitonin gene-related peptide as inflammatory mediator. Springer, Jochen; Geppetti, Pierangelo; Fischer, Axel; Groneberg, David A. Charite Campus-Virchow, Department of Pediatric Pneumology and Immunology, Division of Allergy Research, Humboldt-University Berlin, Berlin, Germany. Pulmonary Pharmacology & Therapeutics (2003), 16(3), 121-130; and *(g)* Pharmacological targets for the inhibition of neurogenic inflammation. Helyes, Zsuzsanna; Pinter, Erika; Nemeth, Jozsef; Szolcsanyi, Janos. Department of Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pecs, Pecs, Hung. Current Medicinal Chemistry: Anti-Inflammatory & Anti-Allergy Agents (2003), 2(2), 191-218 all incorporated by reference herein.

According to various embodiments of a fifth aspect of the present invention are provided combinations of the compounds of the present invention with one or more agents selected from the group consisting of COX-2 inhibitors, NSAIDS, aspirin, acetaminophen, triptans, ergotamine and caffeine for the treatment of migraine.

According to a sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds.

According to the first embodiment of the sixth aspect of the present invention is provided an in vivo non-terminal method of identifying anti-migraine compounds comprising administering a CGRP-receptor agonist to a mammal in an amount capable of inducing an increase in blood flow, followed by administering a test compound in an amount capable of reversing said CGRP-induced increase in blood flow, wherein said mammal is a transgenic mammal with humanized RAMP1 having Trp74 or a mammal endogenously expressing RAMP1 having Trp74.

According to another embodiment of the sixth aspect of the present invention is provided an in vivo non-terminal method of identifying anti-migraine compounds comprising administering to a mammal a test compound prior to the delivery of a

CGRP-receptor agonist wherein said CGRP-receptor agonist is administered in an amount capable of inducing an increase in blood flow and wherein said test compound is administered in an amount capable of suppressing said CGRP-induced increase in blood flow, wherein said mammal is a transgenic mammal with humanized RAMP1 having Trp74 or a mammal endogenously expressing RAMP1 having Trp74.

According to another embodiment of the sixth aspect of the present invention is provided an in vivo non-terminal method of identifying anti-migraine compounds comprising administering to a mammal a CGRP-receptor agonist in an amount capable of inducing an increase in peripheral artery diameter, followed by administering a test compound in an amount capable of reversing said CGRP-induced increase in peripheral artery diameter, wherein said mammal is a transgenic mammal with humanized RAMP1 having Trp74 or a mammal endogenously expressing RAMP1 having Trp74.

According to another embodiment of the sixth aspect of the present invention is provided an in vivo non-terminal method of identifying anti-migraine compounds comprising administering to a mammal a test compound prior to the delivery of a CGRP-receptor agonist wherein said CGRP-receptor agonist is administered in an amount capable of inducing an increase in peripheral artery diameter and wherein said test compound is administered in an amount capable of suppressing said CGRP-induced increase in peripheral artery diameter, wherein said mammal is a transgenic mammal with humanized RAMP1 having Trp74 or a mammal endogenously expressing RAMP1 having Trp74.

According to other embodiments of the sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds as described herein wherein said blood flow is facial blood flow.

According to other embodiments of the sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds as described herein wherein said mammal endogenously expressing RAMP1 having Trp74 is a non-human primate.

According to other embodiments of the sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds

as described herein wherein said mammal endogenously expressing RAMP1 having Trp74 is man.

According to other embodiments of the sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds as described herein wherein said mammal endogenously expressing RAMP1 having Trp74 is a non-human primate and said non-human primate is a marmoset.

According to other embodiments of the sixth aspect of the present invention are provided in vivo non-terminal methods of identifying anti-migraine compounds as described herein wherein said anti-migraine compounds are CGRP-receptor antagonists.

Other embodiments of the present invention may comprise a suitable combination of two or more of the embodiments and/or aspects disclosed herein.

Yet other embodiments of the present invention may comprise a suitable subset of an embodiment and/or aspect disclosed herein.

Still yet other embodiments and aspects of the invention will be apparent according to the description provided below.

Brief Description of the Figures

Figure 1. Schild Analysis.

Dose response of CGRP stimulated cAMP production in the absence (filled squares) and presence (all others) of increasing concentrations (left-to-right) of the CGRP antagonist Example 2. Inset is Schild plot of log dose ratio minus 1 (Y-axis) against log concentration of the antagonist Example 2 (X-axis): Slope = 0.94, K_b = 0.16 nM.

Figure 2. Direct Validation of Facial Blood Flow as Surrogate for Intracranial Artery Dilation in the Rat.

Intravenous delivery of i.v. hαCGRP induces comparable percent increases (100-120% of baseline) in rat middle meningeal artery diameter and rat facial blood flow (left and right striped bars, respectively). Pretreatment with the peptide antagonist CGRP(8-37) produces a 50% inhibition of subsequent i.v. hαCGRP administration for both measures (filled bars). Intracranial artery diameter and facial blood flow

were measured concurrently in each animal (n = 5 rats). Data are mean ± sem * p < 0.05, ** p < 0.01 vs corresponding hαCGRP alone.

Figure 3. Dose-Response for hαCGRP in Non-Human-Primate Laser Doppler Facial Blood Flow.

Delivery of hαCGRP induces dose-dependent increase in laser Doppler facial blood flow in non-human primates (e.g., common marmoset). Animals (n= 6) received increasing doses of hαCGRP at 30 min intervals. Data are peak % change from baseline ± sem, with each animal serving as its own control.

Figure 4. Inhibitition of CGRP-Induced Changes in Non-Human Primate Facial Blood Flow.

The novel CGRP antagonist Example 2 (filled bars) delivered prior to hαCGRP (striped bar), dose-dependently inhibits the CGRP-induced increase in laser Doppler facial blood flow. Vehicle (open bar) was without effect. Data are mean ± sem (n = 5-6 primates per group). *p < 0.05 compared CGRP alone.

Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure.

In contrast to the dose-dependent inhibition of primate facial blood flow (see Figure 4.), Example 2 has negligible effect on blood pressure (parallel studies in separate animals, n=6). Animals received repeat doses of Example 2 at 20 min intervals. BP data are mean ± sem over 20 min period measured by arm cuff

Detailed Description of the Invention

The description of the invention herein should be construed in congruity with the laws and principals of chemical bonding. For example, it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location.

As used herein, "heterocyclic" or "heterocycle" includes cyclic moieties containing one or more heteroatoms, (*e.g.*, O, N or S) said heterocycles include those that are aromatic and those that are not, *i.e.*, "alicyclic", unless otherwise specified.

As used herein, the term "fused bicyclic system" when describing for example a 5.6-fused bicyclic system containing 1 to 4 nitrogen atoms includes aromatic and

alicyclic systems, *e.g.* indolizine, indole, isoindole, 3H-indole, indoline, indazole or benzimidazole.

If a substitutent is named generically, then any and all species of that genus comprise that aspect of the invention. For example, a substituent generically named as "pyrrolonyl" (the radical of "pyrrolone", a pyrrole having a carbonyl) includes pyrrol-2-onyls wherein the carbonyl is adjacent to the nitrogen and pyrrol-3-onyls wherein the carbonyl and nitrogen have an intervening methylene.

Similarly, the present invention comprises that a substituent may be attached at any and all suitable points of attachement on said substituent unless otherwise specified.

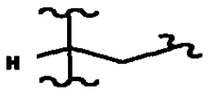
However, it is also understood that the compounds encompassed by the present invention are those that are chemically stable, i.e., heteroalicyclic substituents of the present invention should not be attached in such a way that a heteroatom in said heteroalicyclic substituent is alpha to a point of attachment wherein said point of attachment is also a heteroatom.

An embodiment or aspect which depends from another embodiment or aspect, will describe only the variables having values or provisos that differ from the embodiment or aspect from which it depends. If for example a dependent embodiment only addresses R^2, then the variables and provisos not related to R^2 should reflect that of the embodiment from which it depends.

If a variable is quantified with a value of zero, then a bond attaching said variable should no longer be represented.

As used herein, "alkylene" means a divalent alkane, *i.e.*, an alkane having two hydrogen atoms removed from said alkane (said hydrogen removed from two different carbon atoms when said alkane contains more than one carbon atom), *e.g.*, $-CH_2CH_2CH_2-$.

As used herein, "alkylidene" means an alkane having two hydrogen atoms removed from one carbon atom in said alkane, *e.g.* ,



It should be understood that the alternating double bond designations in the six-membered ring of the 5,6-membered fused structure represented in Formula (I) are relative and represent the delocalized π orbital electrons of said ring.

As used herein, "aryl" or "ar-" includes phenyl or napthyl.

As used herein, "heterocyclic" or "heterocyclo" includes both heteroaryl and heteroalicyclic.

As used herein, "halo" or "halogen" includes fluoro, chloro, bromo and iodo and further means one or more of the same or different halogens may be substituted on a respective moiety.

Unless specificied otherwise, acyclic hydrocarbons such as alkyl, alkoxy, alkenyl and alkynyl may be branched or straight chained.

It is to be understood that the present invention may include any and all possible stereoisomers, geometric isomers, diastereoisomers, enantiomers, anomers and optical isomers, unless a particular description specifies otherwise.

As used herein, "Trp74", means that the 74th residue in RAMP1 is tryptophan (Mallee et al. *J Biol Chem* 2002, *277*, 14294-8) incorporated by reference herein.

As used herein "anti-migraine compound" includes any compound, peptide or peptide fragment (modified or unmodified) capable of reversing or attenuating CGRP-receptor mediated vasodilation, (*e.g.*, CGRP-receptor antagonists).

As used herein "test compound" includes any compound, peptide or peptide fragment (modified or unmodified) being tested to determine if it is capable of reversing or attenuating CGRP-receptor mediated vasodilation, (*e.g.*, putative CGRP-receptor antagonists).

As used herein, "CGRP-receptor agonist" includes any compound, peptide or peptide fragment (modified or unmodified) capable of inducing CGRP-receptor mediated vasodilation particularly by example αCGRP or βCGRP; other members of the calcitonin family, *e.g.* adrenomedullin; N-terminal CGRP fragments, *e.g.* CGRP(1-12) CGRP(1-15) and CGRP(1-22); C-terminal amide (NH2) versions of CGRP *e.g.*, CGRP(1-8+NH2), CGRP(1-13+NH2) or CGRP(1-14+NH2); and non-naturally occurring CGRP analogues *e.g.*, [Ala^1 ψ(CH2NH)Cys^2]hCGRP which contains a pseudopeptide bond between Ala^1 and Cys^2. *See* Maggi CA, Rovero P, Giuliani S, Evangelista S, Regoli D, Meli A. Biological activity of N-terminal fragments of calcitonin gene-related peptide. Eur J Pharmacol. 1990 Apr 10;179(1-

2):217-9; Qing X, Wimalawansa SJ, Keith IM. Specific N-terminal CGRP fragments mitigate chronic hypoxic pulmonary hypertension in rats. Regul Pept. 2003 Jan 31;110(2):93-9; and Dennis T, Fournier A, St Pierre S, Quirion R. Structure-activity profile of calcitonin gene-related peptide in peripheral and brain tissues. Evidence for receptor multiplicity. J Pharmacol Exp Ther. 1989 Nov;251(2):718-25 incorporated by reference herein.

The compounds of this invention may exist in the form of pharmaceutically acceptable salts. Such salts may include addition salts with inorganic acids such as, for example, hydrochloric acid and sulfuric acid, and with organic acids such as, for example, acetic acid, citric acid, methanesulfonic acid, toluenesulfonic acid, tartaric acid and maleic acid. Further, in case the compounds of this invention contain an acidic group, the acidic group may exist in the form of alkali metal salts such as, for example, a potassium salt and a sodium salt; alkaline earth metal salts such as, for example, a magnesium salt and a calcium salt; and salts with organic bases such as a triethylammonium salt and an arginine salt. In the case of a sublingual formulation a saccharin salt or maleate salt may be of particular benefit. The compounds of the present invention may be hydrated or non-hydrated.

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. The compounds of this invention may also be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, all using dosage forms well known to those skilled in the pharmaceutical arts. The compounds can be administered alone, but generally will be administered with a pharmaceutical carrier selected upon the basis of the chosen route of administration and standard pharmaceutical practice. Compounds of this invention can also be administered in intranasal form by topical use of suitable intranasal vehicles, or by transdermal routes, using transdermal skin patches. When compounds of this invention are administered transdermally the dosage will be continuous throughout the dosage regimen.

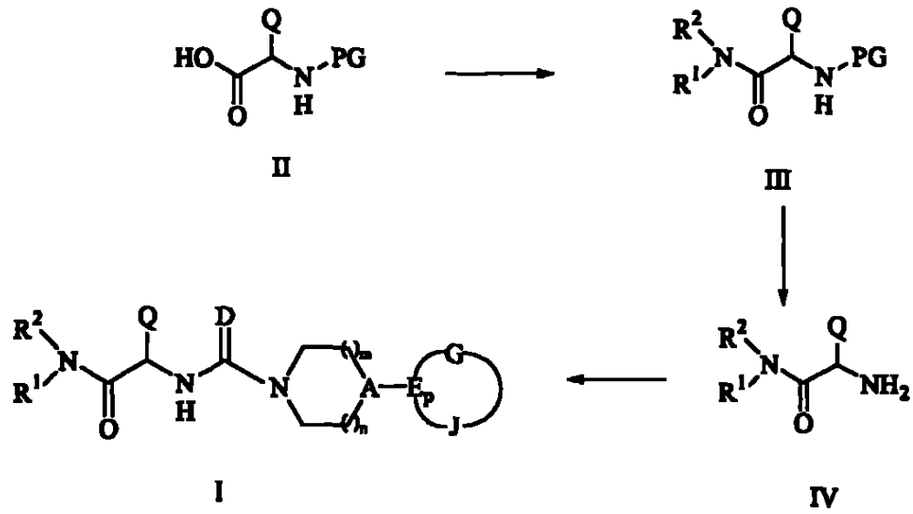
While dosing from 0.01 mg/kg to 30 mg/kg is envisaged for compounds of the present invention, the dosage and dosage regimen and scheduling of a compounds of the present invention must in each case be carefully adjusted, utilizing sound

professional judgment and considering the age, weight and condition of the recipient, the route of administration and the nature and extent of the disease condition. In accordance with good clinical practice, it is preferred to administer the instant compounds at a concentration level which will produce effective beneficial effects without causing any harmful or untoward side effects.

Synthesis

Compounds of the present invention may be synthesized according to the general schemas provided below. Variables provided in the schema below are defined in accordance with the description of compounds of the above Formula unless otherwise specified. The compounds of the present invention may be prepared according to Scheme 1 or Scheme 2. It may also be possible to use variations of said schemes to prepare the compounds of the present inventions, said variations known to those of ordinary skill in the art.

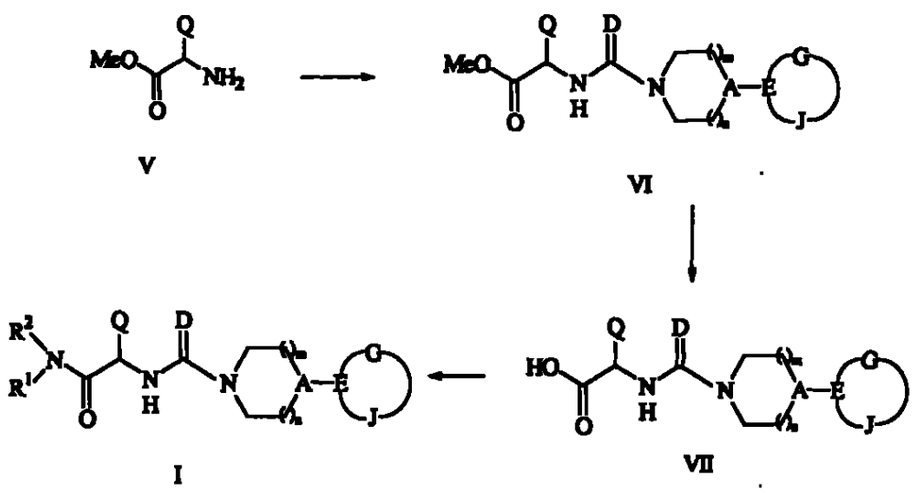
Scheme 1. Synthesis of Formula I Compounds



The synthesis described in Scheme 1 begins with a compound of Formula II, which is an amino acid with a protected amino terminus. Common amino protecting groups (PG) include BOC, CBZ, and FMOC and their addition and removal are well known in the field. The carboxylic acid moiety of a Formula II compound is coupled

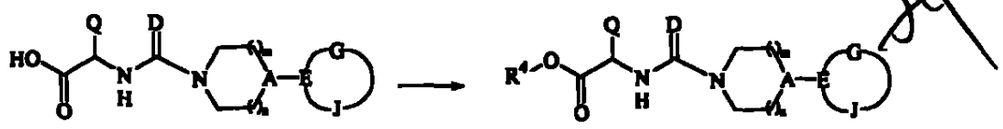
with an amine of formula HNR^1R^2 using standard peptide coupling reagents to form an amide of Formula III. The amino protecting group is removed resulting in a Formula IV compound. This compound is then coupled with an amine of Formula V (see below) in a mixed urea or urea isostere reaction, generating a Formula I compound. Mixed urea formation is conveniently carried using phosgene, disuccinimidyl carbonate, carbonyl diimidazole or other equivalents. Formation of urea isosteres, such as cyanoguanidines and sulfonylguanidines, are known in the literature.

Scheme 2. Synthesis of Formula I Compounds



The synthesis described by Scheme 2 begins with a compound of Formula V, which is an amino acid with a protected carboxylate terminus. The protection is generally a methlyl ester, but other protecting groups such as ethyl, t-butyl, and benzyl esters may also be used. The Formula V compound is coupled with an amine of Formula VIII (see below) in a mixed urea or urea isostere reaction, as above, to generate a Formula VI compound. The Formula VI compound is converted to a free acid compound of Formula VII which is then coupled with an amine of Formula HNR^1R^2 to generate a Formula I compound.

Scheme 3. Synthesis of Formula I Compounds

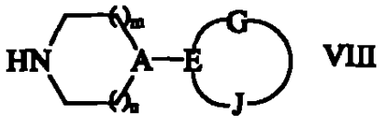


VII I

The synthesis described by Scheme 3 begins with a compound of Formula VII from Scheme 2. The Formula V compound is coupled with an alcohol, R^4-OH. Such ester-forming reactions are well known in the art and can be carried out, for example, with carbodiimide coupling agents such as N,N-dicyclohexylcarbodiimide. In addition, it is often advantageous, especially for esters of secondary and tertiary alcohols, to include additives that accelerate acylations such as 4-dimethylaminopyridne.

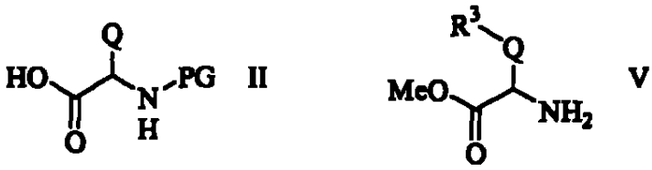
Preparation of HNR^1R^2 and Formula VIII amines

Formula VIII and HNR^1R^2 amines are commercially available, made by literature methods or described herein.



VIII

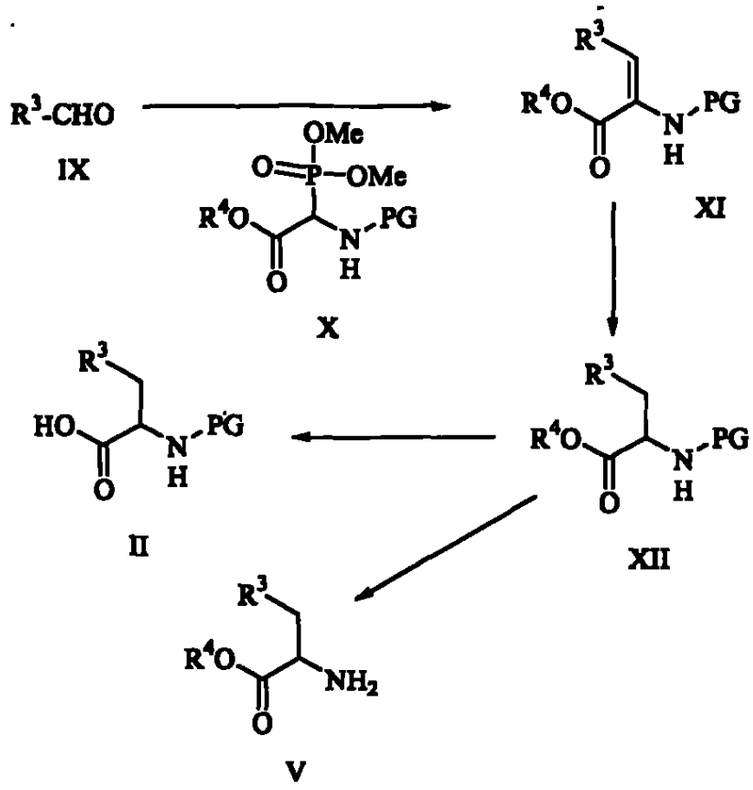
Preparation of Formula II and Formula V amino acids



II V

Formula II and Formula V amino acids may be commercially available or made as described in Scheme 4.

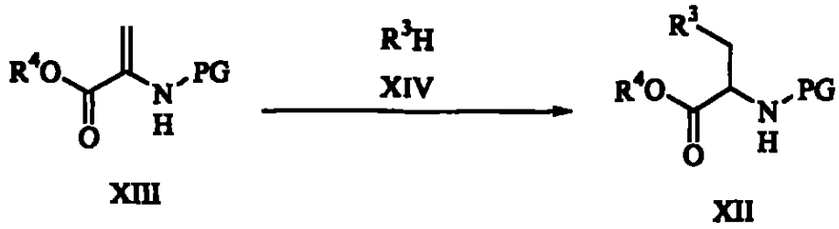
Scheme 4. Synthesis of Formula II and Formula V Compounds



The synthesis described in Scheme 4 begins with an aldehyde of Formula IX, which is reacted with a glycine phosphonate of Formula X in a Wadsworth-Emmons coupling reaction. The compound of Formula X is deprotonated with a base such as diazabicycloundecene or tetramethylguanidine or other organic or inorganic bases well known in the art. The double bond of the resulting Formula XI compound is reduced to give compounds of Formula XII. Reduction can be carried out to give either a racemate or by use of a stereoselective catalyst to give either enantiomer of Formula XII. Such reductions can result from transfer hydrogenation from hydrogen donors such as formic acid or cyclohexadiene, or hydrogenation using gaseous hydrogen, both in the presence of a suitable catalyst. Compounds of Formula II are prepared by acid or base hydrolysis of the ester. Compounds of Formula V are prepared by removal of the protecting group (PG) using methods well known in the art.

Other amino acid derivatives of Formula XII may be prepared as shown in Scheme 5.

Scheme 5. Synthesis of Formula XII

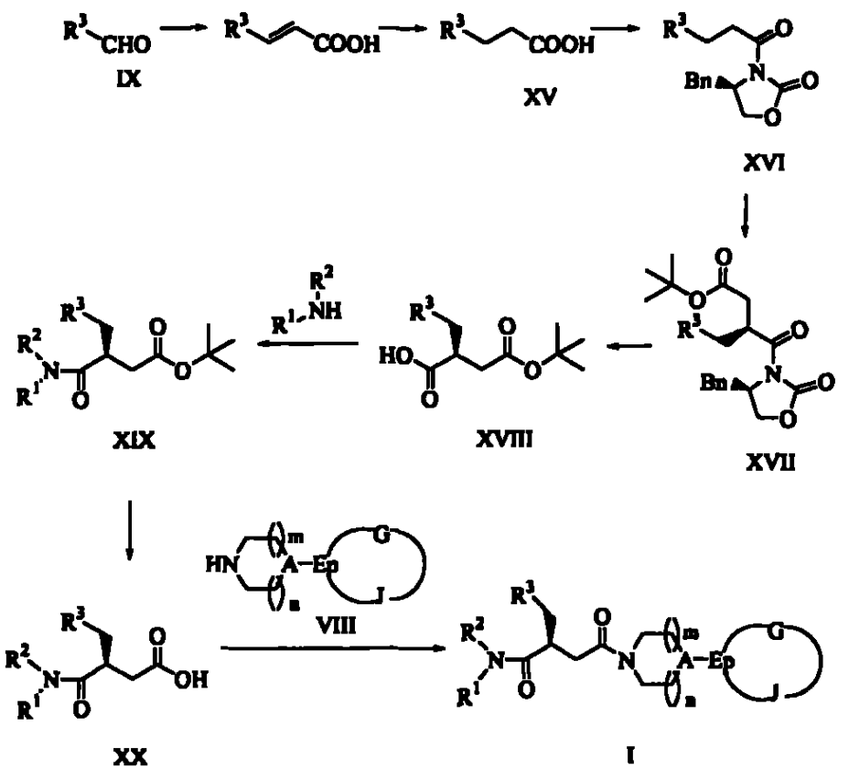


XIII XII

Where, for the purposes of Scheme 5, compounds of Formula XIV are nucleophilic compounds such as amines or alcohols that are able to participate in a Michael Reaction with a compound of Formula XIII as shown.

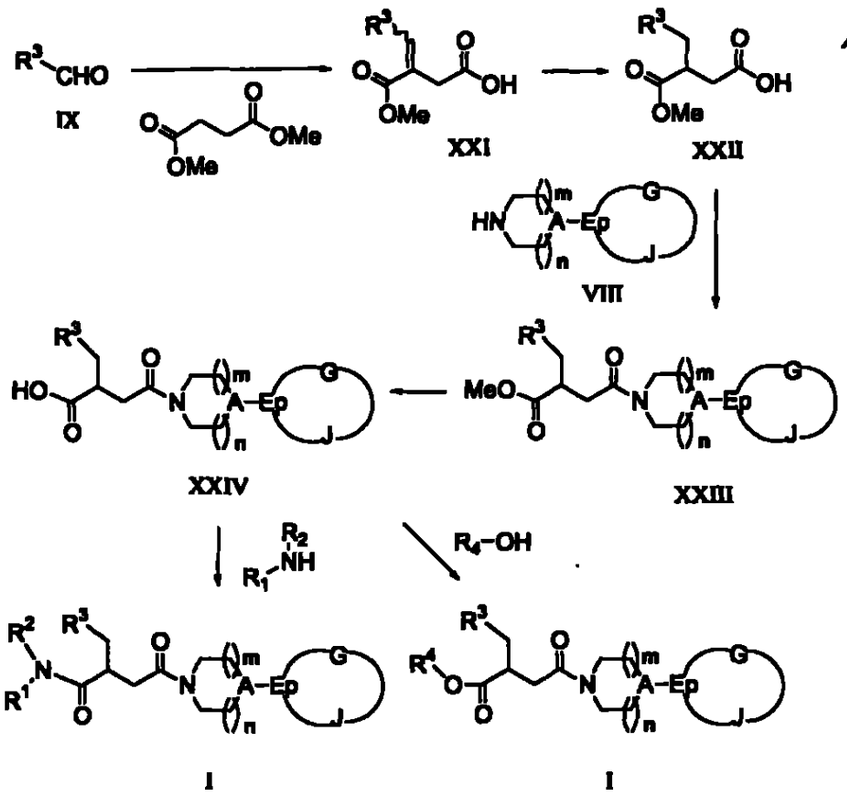
Other compounds of Formula I may be prepared according to Scheme 6 or Scheme 7. It may also be possible to use variations of said schemes to prepare the compounds of the present inventions, said variations known to those of ordinary skill in the art.

Scheme 6. Synthesis of Formula I Compounds



The synthesis described in Scheme 6 begins with commercially available or synthesized aldehydes. The two-carbon homologation and double-bond reduction which are well-known in the literature and lead to compounds of Formula XV. Some Formula XV compounds are also commercially available and others may be prepared by other methods well known in the art. Preparation of compounds of Formula XVI and XVII are known in the literature as substrates and products of the Evans chiral asymmetric synthesis. Hydrolysis leads to compounds of Formula XVIII. As with compounds of Formula VII in Scheme 2, these carboxylic acids can react with amines of formula R^1R^2NH to afford compounds of Formula XIX using well known amide coupling protocols. Hydrolysis of the *tert*-butyl ester leads to compounds of Formula XX, which can be further coupled with compounds of Formula VIII to afford Formula I compounds.

Scheme 7. Synthesis of Formula I Compounds

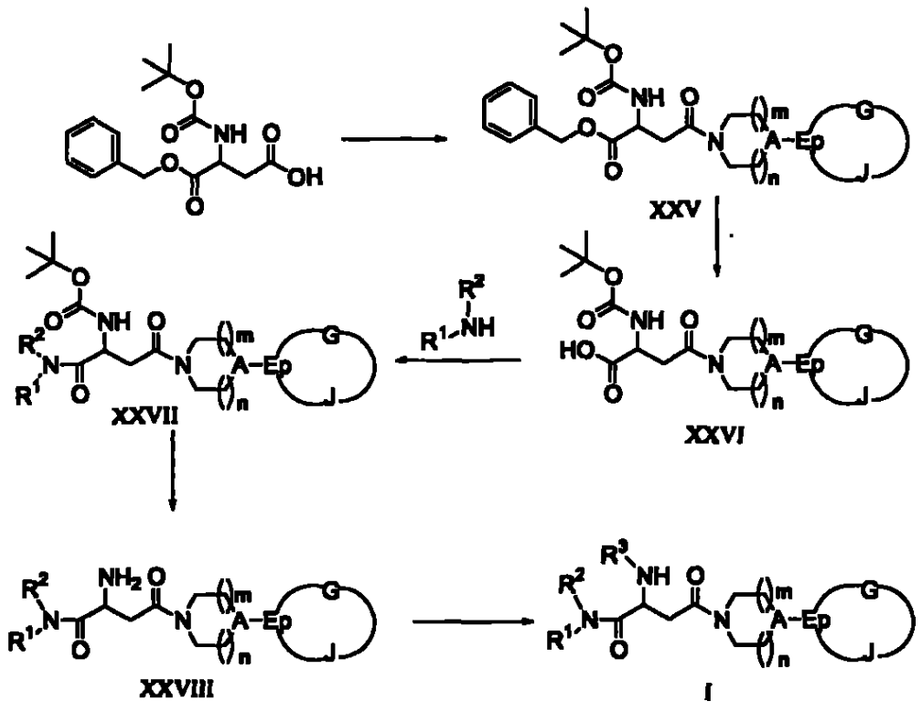


Scheme 7 also starts with commercially available or synthesized aldehydes. These are reacted with dimethyl succinate in the presence of bases to give compounds of Formula XXI. The double bond of the Formula XXI compound is reduced to give compounds of Formula XXII. Reduction can be carried out to give either a racemate or by use of a stereoselective catalyst to give either enantiomer of Formula XXII. Such reductions can result from transfer hydrogenation from hydrogen donors such as formic acid or cyclohexadiene, or hydrogenation using gaseous hydrogen, both in the presence of a suitable catalyst. Amide coupling with amines of Formula VIII lead to compounds of Formula XXIII using well known amide synthesis protocols. Hydrolysis of methyl ester leads to Formula XXIV compounds, which are further coupleded with various amines or alcohols to give amides of Formula I and esters of Formula I, respectively.

Compounds of Formula I may also be prepared according to Scheme 8.

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Scheme 8. Synthesis of Formula I Compounds

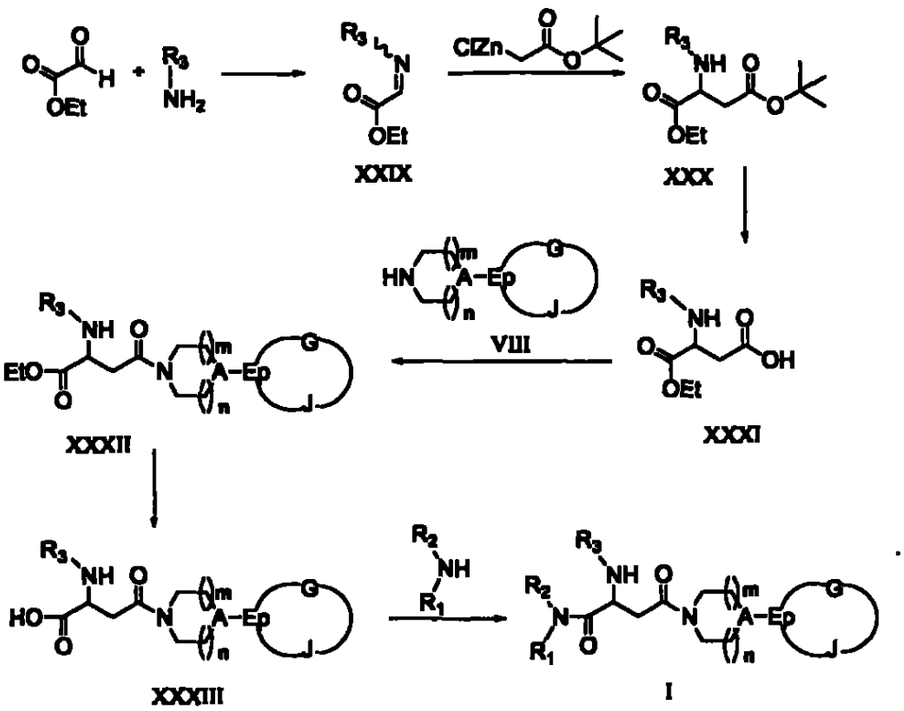


The synthesis described in Scheme 8 begins with a commercially available N-*tert*-butyloxycarbonyl-L-aspartic acid benzyl ester. Differently protected aspartic acid derivatives may also be used for synthetic convenience. The beta carboxyl group is coupled with amines of Formula VIII using standard peptide coupling protocols. The alpha-carboxyl protecting group of the Formula XXV compound is removed by hydrogenolysis giving compounds of Formula XXVI. These are further coupled with amines of the formula HNR^1R^2 to give compounds of formula XXVII. The amino protecting group is removed by treatment with strong acids such as trifluoroacetic acid or hydrogen chloride in organic solvents. The resulting compounds of Formula XXVIII are then reacted with a variety of electrophilic reagents to generate Formula I compounds. For example, they can be coupled with halo-aromatic compounds using known methods involving heating at various temperatures or by catalysis with transition metals such as palladium or copper, either in stoichiometric amounts or as catalysts. They can also react with various aldehydes or ketones under reductive alkylation conditions, well described in the art. They can also react with isocyanates,

acyl chlorides, or carbamoyl chlorides to generate urea, amide or carbamate derivatives, respectively. It is understood that the sequence of the modifications described above can be changed depending on the selection of protecting groups and the order of their removal.

Compounds of Formula I may also be prepared according to Scheme 9.

Scheme 9. Synthesis of Formula I Compounds



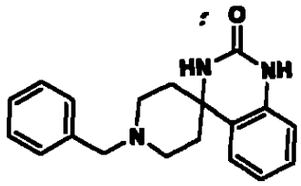
The synthesis described in Scheme 9 begins with an imine of Formula XXIX, prepared by condensation of ethyl glyoxalate and amines of formula R^3-NH_2. These are reacted with 2-*tert*-butoxy-2-oxoethylzinc chloride to give compounds of Formula XXX. Treatment wit strong acids removes the *tert*-butyl ester protecting group to give free acids of Formula XXXI which are coupled to amines of Formula VIII to yield compounds of Formula XXXII. The ethyl ester is hydrolyzed with a metal hydroxide salt or aqueous base to give free alpha-acids of Formula XXXIII. These, in turn are coupled with amines of the formula HNR^1R^2 to give compounds of formula I.

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Ureidoamide Intermediates and Examples

General. ^{1}H- and ^{13}C-NMR spectra were run on a Bruker 500 or 300 MHz instrument and chemical shifts were reported in ppm (δ) with reference to tetramethylsilane (δ = 0.0). All evaporations were carried out under reduced pressure. Unless otherwise stated, LC/MS analyses were carried out on a Shimadzu instrument using a YMC C18 column (3 x 50 mm) employing a 2 min linear gradient of 0% to100% solvent B in A in a 3 min run. For LC/MS and for Shimadzu Preparative HPLC system, Solvent A-was:10% methanol/90% water/0.1% trifluoroacetic acid, and solvent B was 90% methanol/10% water/0.1% trifluoroacetic acid with a UV detector set at 220 nm.

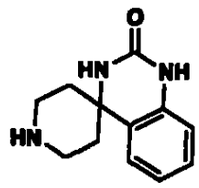
1-Benzyl-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'(1'H)-quinazoline



Polyphosphoric acid (113 g) was heated to 100-110°C and stirred while 1-benzyl-piperidin-4-one (9.27 ml, 50 mmol) was added. Immediately afterwards, phenyl urea (9.55 g, 70. mmol) was added in portions small enough to avoid excessive foaming. The mixture was heated at 150-160°C overnight. Water (200 mL) was then added slowly to the mixture which had been allowed to cool to 100-110°C (at lower temperatures the mixture becomes too viscous to stir). The resulting solution was neutralized with 10N NaOH to ca. pH 8, and then extracted wth chloroform. The organic phase was dried over magnesium sulfate and then concentrated to give the crude product which was purified by flash column chromatography on silica gel (6:4 ethyl acetate/hexanes) to give the desired product (9.0 g, 58%). Mass spec.: 308.25 $(MH)^{+}$.

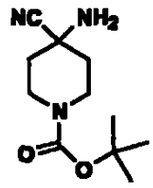
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2',3'-dihydro-2'-oxospiro-[piperidine-4,4'(1'H)-quinazoline



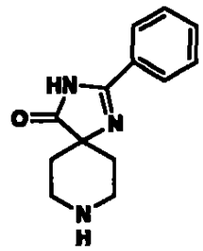
To a solution of 1-benzyl-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'(1'H)-quinazoline (1.00 g) in degassed methanol (50 ml) and 6N hydrochloric acid (2.0 ml) was added 10% palladized charcoal (150 mg). The mixture was shaken on a Parr apparatus under an atmosphere of hydrogen at 60 psi overnight. LC/MS showed incomplete reaction. More 10% palladized charcoal (200 mg) was added, and the mixture was shaken for 2 more days. At that point, all starting material was consumed. The mixture was filtered and the filtrate concentrated to give 531 mg of the desired compound (64%). Mass spec.: 218.12 $(MH)^+$.

4-Amino-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester



To a well stirred solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (9.0 g, 45.3 mmol) in methanol was added ammonium chloride (2.66 g, 49.8 mmol) at room temperature and stirred for 1 h. Sodium cyanide (2.44 g, 49.8 mmol) was added and stirring was continued for additional 16 h. The reaction mixture was quenched with 5% aqueous sodium hydrogencarbonate (50 mL), diluted with water, and the methanol removed by rotary evaporation. The cyanoamine was extracted with methylene chloride (3x 100 mL), dried over sodium sulfate, and the solvents evaporated to give the desired compound as an oil in 91% yield. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.95 - 3.90 (m, 1 H), 3.80 - 3.71 (m, 1 H), 3.42 - 3.06 (m, 2 H), 2.04 - 1.94 (m, 1 H), 1.71 - 1.50 (m, 3 H). Mass spec.: 226 $(MH)^+$.

2-Phenyl-1,3,8-triaza-spiro[4.5]dec-1-en-4-one, hydrochloride

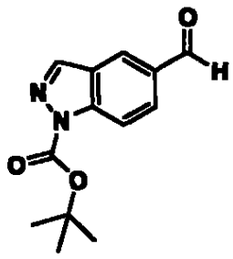


To a solution of 4-amino-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (1.0 g, 4.44 mmol) in methylene chloride (30 mL) was added triethylamine (1.24 mL, 8.88 mol), followed by benzoyl chloride (936 mg, 6.66 mmol). After 30 min, 4-(dimethylamino)pyridine (40 mg, 0.33 mmol) was added and stirring continued for additional 12 h. The reaction mixture was then quenched with 1M sodium hydroxide (10 mL), diluted with ethyl acetate (100 mL), and separated. The organic layer was washed sequentially with 1M sodium hydroxide (40 mL), aqueous sodium hydrogencarbonate (50 mL), and brine (50 mL) then dried over sodium sulfate. The desired product, 4-benzoylamino-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester was obtained in 90% yield through crystallization using 30% ethyl acetate in hexane as a solvent.

To a solution of 4-benzoylamino-4-cyano-piperidine-1-carboxylic acid *tert*-butyl ester (1.3 g, 4 mmol) in ethanol (10 mL) was added 6M sodium hydroxide (1.5 mL) followed by 30% hydrogen peroxide. The reaction mixture was then refluxed for 3 h. The reaction mixture was then diluted with water (30 mL), and the ethanol removed. The residue was diluted with ethyl acetate (100 mL). The organic phase was washed with brine (30 mL) and dried over sodium sulfate. The desired product, 4-oxo-2-phenyl-1,3,8-triaza-spiro[4.5]dec-1-ene-8-carboxylic acid *tert*-butyl ester was obtained in 80% yield through crystallization from 30% ethyl acetate in hexane. The *tert*-butyl ester was then dissolved in methylene chloride (5 mL) and a saturated solution of hydrogen chloride in dioxane (25 mL)was added. After 2 h, the solvent was removed to give 2-phenyl-1,3,8-triaza-spiro[4.5]dec-1-en-4-one, hydrochloride as white powder in 95% yield. ^{1}H-NMR (500 MHz, CD_3OD): δ 8.23 - 8.21 (m, 2 H), 7.96 - 7.92 (m, 1 H), 7.79 - 7.76 (m, 2 H), 3.68 - 3.64 (m, 3 H), 3.31 - 3.30 (m, 1 H), 2.47 - 2.44 (m, 4 H). Mass spec.: 230 $(MH)^+$.

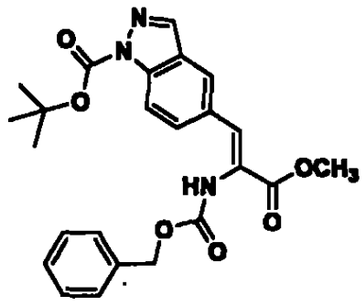
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5-Formyl-indazole-1-carboxylic acid *tert*-butyl ester



A methylene chloride (2 mL) solution of di-*tert*-butyldicarbonate (388 mg, 1.78 mmol) was added dropwise at room temperature to a solution of 1*H*-indazole-5-carbaldehyde (273 mg, 1.87 mmol), 4-dimethylaminopyridine (114 mg, 0.94 mmol), and triethylamine (0.26 mL, 1.87 mmol) in methylene chloride (10 mL). The resulting bright yellow solution was stirred at room temperature for 16 h. Solvents were removed *in vacuo* and the residue was subjected to flash chromatography with silica gel (25 g) and ethyl acetate/hexanes (1:1) containing 1% triethylamine as eluent to afford the title compound as a brownish yellow liquid (414 mg, 90%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.08 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 1.71 (s, 9H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ 191.8, 149.0, 142.5, 140.6, 133.0, 128.3, 126.4, 125.8, 115.3, 85.7, 27.8.

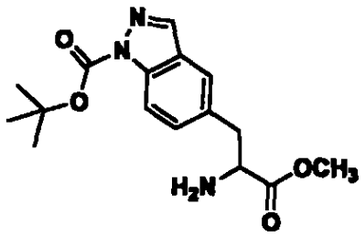
5-(2-Benzyloxycarbonylamino-2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester



A solution of *N*-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (5.50 g, 16.6 mmol) and tetramethylguanidine (1.99 mL, 15.9 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred at -78°C for 20 min. To this was added a solution of 5-formyl-indazole-1-carboxylic acid *tert*-butyl ester (3.72 g, 15.1 mmol) in tetrahydrofuran (25 mL) slowly via syringe over 10 min. The reaction mixture

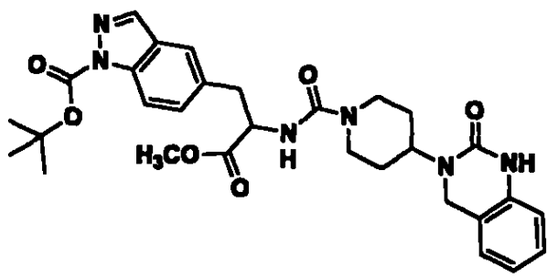
was stirred at -78°C for 4 h and then allowed to warm to room temperature overnight. The solvent was evaporated and the resulting residue subjected to flash column chromatography on silica gel (1:2 ethyl acetate/hexane) giving the title compound as a white foam (5.77 g, 85%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.09 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.30 (br s, 5H), 6.43 (br s, 1H), 5.09 (s, 2H), 3.84 (s, 3H), 1.72 (s, 9H). Mass spec.: 452 $(MH)^+$.

(±)-5-(2-Amino-2-methoxycarbonyl-ethyl)-indazole-1-carboxylic acid *tert*-butyl ester



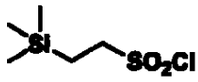
A mixture of 5-(2-benzyloxycarbonylamino-2-methoxycarbonyl-vinyl)-indazole-1-carboxylic acid *tert*-butyl ester (524 mg, 1.16 mmol) and 10% palladium on carbon (60 mg) in methanol (20 mL) was shaken for 4.5 h under 50 psi hydrogen gas using a Parr hydrogenator. The reaction mixture was evacuated and purged with nitrogen. Then, the reaction mixture was filtered through a pad of celite and the pad was rinsed with several portions of methanol. The methanol filtrate was evaporated to give the title compound (351 mg, 95%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.12-8.10 (m, 2H), 7.55 (br s, 1H), 7.37 (dd, J = 8.9, 1.5 Hz, 1H), 3.77-3.75 (m, 1H), 3.70 (s, 3H), 3.19 (dd, J = 13.7, 5.5 Hz, 1H), 2.99 (dd, J = 13.7, 8.0 Hz, 1H), 1.72 (s, 9H). Mass spec.: 320 $(MH)^+$.

(±)-5-(2-Methoxycarbonyl-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-ethyl)-indazole-1-carboxylic acid *tert*-butyl ester



A solution of 5-(2-amino-2-methoxycarbonyl-ethyl)-indazole-1-carboxylic acid *tert*-butyl ester (307 mg, 0.96 mmol), *N,N*-disuccinimidyl carbonate (246 mg, 0.961 mmol), and *N,N*-diisopropylethylamine (0.67 mL, 3.84 mmol) in methylene chloride was stirred for 30 min at room temperature. 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one (238 mg, 1.03 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue subjected to flash chromatography using methylene chloride/methanol/triethylamine (93:5:2) as eluent, giving the product (259 mg, 47%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.13-8.10 (m, 2H), 7.48 (br s, 1H), 7.31 (dd, J = 8.8, 1.6 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.82 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H), 4.98 (d, J = 7.7 Hz, 1H), 4.87-4.81 (m, 1H), 4.58-4.49 (m, 1H), 4.26 (s, 2H), 4.05-3.97 (m, 2H), 3.74-3.67 (m, 4H), 3.29-3.23 (m, 2H), 2.93-2.84 (m, 2H), 1.76-1.62 (m, 1H), 1.70 (s, 9H), 1.48-1.42 (m, 1H). Mass spec.: 577 $(MH)^+$.

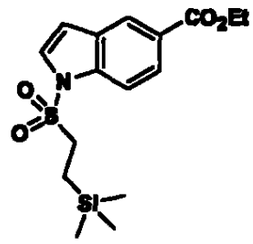
2-Trimethylsilanyl-ethanesulfonyl chloride



Sulfuryl chloride (43 ml, 539 mmol) was added in 3 min to a clear solution of triphenylphosphine (129 g, 490 mmol) in methylene chloride (200 mL) at 0°C in a flame-dried three-neck round bottom flask. After stirring at 0°C for 5 min, the ice-water bath was removed and sodium 2-trimethylsilylethanesulfonate (50 g, 245 mmol) was added in portions over 10 min. The resulting white suspension was stirred at room temperature for 16 h, then it was filtered through a pad of celite. The filtrate was concentrated to ca 50 mL, ethyl acetate/hexanes (1:3, 1000 mL) and celite (40 g) were added. The mixture was stirred at room temperature for 15 min and filtered through a pad of celite. Solvents were removed *in vacuo* and the residue was loaded onto a pre-wetted column with silica gel (300 mL) using 1:3 ethyl acetate/hexanes as the eluent. Solvents were removed and the title compound was obtained as a light tan liquid (41.9g, 85%). If not used immediately, the final product should be stored under nitrogen in the freezer or refrigerator to minimize decomposition. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.61-3.57 (m, 2H), 1.32-1.27 (m, 2H), 0.10 (s, 9H).

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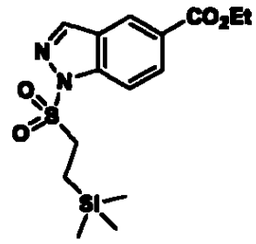
1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carboxylic acid ethyl ester



A solution of 1*H*-indole-5-carboxylic acid ethyl ester (10.31g, 58.8 mmol) in dimethylformamide (50 mL) was added dropwise at 0°C to a mixture of sodium hydride (1.83g, 76.4 mmol) in dimethylformamide (150 mL). The resulting mixture was stirred at 0°C for 30 min, then a solution of 2-trimethylsilanyl-ethanesulfonyl chloride (17.7 g, 88.2 mmol) in dimethylformamide (100mL) was added slowly at 0°C to the above mixture. After 2 h, sat. aqueous ammonium chloride (200 mL) was added, and the mixture was extracted with ethyl acetate (300 mL). After separation, the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine (3 × 150 mL), and dried over anhydrous sodium sulfate. Solvents were removed *in vacuo* and the residue was subjected to flash chromatography on silica gel using 1:1.5 methylene chloride/hexanes as eluent to afford the title compound as a white solid (15.8 g, 79%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.36 (d, J = 1.5 Hz, 1H), 8.03 (dd, J = 9.0, 2.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 3.5 Hz, 1H), 6.75 (d, J = 3.5 Hz, 1H), 3.94 (s, 3H), 3.21 – 3.18 (m, 2H), 0.84 – 0.80 (m, 2H), -0.06 (s, 9H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 167.3, 137.7, 130.3, 128.3, 125.9, 125.5, 124.0, 112.8, 108.3, 52.2, 51.2, 10.1, -2.1. Mass spec. 354.12 $(MH)^+$.

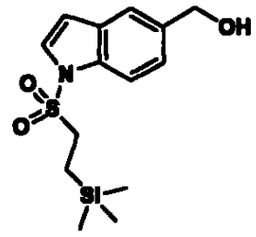
Similarly prepared:

1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indazole-5-carboxylic acid ethyl ester



^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.51 (s, 1H), 8.34 (s, 1H), 8.21 (dd, J = 8.9, 1.5 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 3.96 (s, 3H), 3.42 – 3.39 (m, 2H), 0.86 – 0.82 (m, 2H), -0.02 (s, 9H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 166.4, 143.1, 141.2, 130.1, 126.5, 125.0, 124.2, 112.9, 52.5, 51.3, 9.8, -2.1. Mass spec. 355.13 $(MH)^+$.

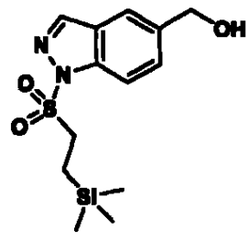
[1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-methanol



A solution of diisobutylaluminum hydride (82.9 mL, 1M in toluene, 82.9 mmol) was added slowly at 0°C to the solution of 1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carboxylic acid ethyl ester (8.81g, 25.9 mmol) in toluene (200mL). After it was stirred at 0°C for 45 min, the reaction was quenched by the addition of methanol (26mL), pulverized sodium sulfate decahydrate (194 g) and celite (26 mL). The mixture was warmed up to room temperature in 1h and filtered through a pad of celite. Solvents were removed *in vacuo* to afford the title compound as a very viscous liquid, which solidified upon cooling. A white solid (8.08 g, 100% yield). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.44 (d, J = 3.7 Hz, 1H), 7.35 (dd, J = 8.6, 1.5 Hz, 1H), 6.66 (d, J = 3.7 Hz, 1H), 4.79 (s, 2H), 3.18 – 3.14 (m, 2H), 1.73 (s, 1H), 0.85 – 0.82 (m, 2H), -0.06 (s, 9H). Mass spec. 312.14 $(MH)^+$.

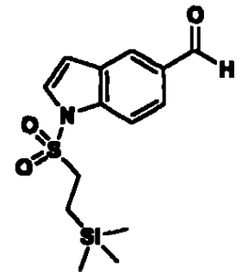
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[1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-methanol



A solution of 1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazole-5-carboxylic acid ethyl ester (azeotropically dried with toluene (2x), 5.77g, 16.9 mmol) in tetrahydrofuran (50 mL) was added at 0°C to a mixture of lithium borohydride (3.68g, 169 mmol) in tetrahydrofuran (100 mL). The mixture was warmed up to room temperature and stirred for 14h. It was cooled to 0°C and lithium borohydride (3.5g) was added. The mixture was warmed up to room temperature and stirred for 14h. It was re-cooled to 0°C and sat. aqueous ammonium chloride (25 mL) was added slowly. The resulted white suspension was filtered through a pad of celite, solvents were removed and the residue was subjected to flash chromatography using ethyl acetate/hexanes (1:1.5) with 1% triethylamine to afford the title compound as a white solid (3.8g, 72%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.41 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 7.61 (dd, J = 8.5, 1.2 Hz, 1H), 4.76 (s, 2H), 3.49 – 3.46 (m, 2H), 0.76 – 0.72 (m, 2H), -0.03 (s, 9H); ^{13}C-NMR (CD_3OD, 125 MHz) δ 141.2, 140.9, 138.3, 129.2, 125.8, 119.6, 112.7, 63.8, 50.8, 9.9, -3.2. Mass spec. 313.12 $(MH)^+$.

1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carbaldehyde

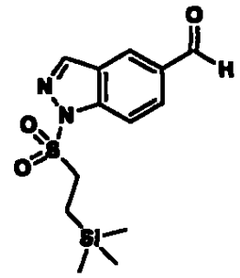


A solution of [1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-methanol (2.1g, 6.74 mmol) in methylene chloride (30 mL) was added at 0°C to a mixture of activated manganese dioxide (22g, azeotropically dried with toluene (2x)) and

methylene chloride (70 mL) in a 500 mL round bottom flask. The reaction mixture was stirred at 0°C for 30 min and filtered through a pad of celite. Solvents were removed *in vacuo* to afford the title compound as a white solid (1.8g, 80%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.06 (s, 1H), 8.15 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.87 (dd, J = 8.6, 1.5 Hz, 1H), 7.54 (d, J = 3.4 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 3.24 – 3.20 (m, 2H), 0.86 – 0.82 (m, 2H), -0.06 (s, 9H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 191.9, 138.5, 132.3, 130.7, 128.8, 125.3, 125.1, 1134.6, 108.4, 51.4, 10.2, -2.1. Mass spec. 310.12 $(MH)^+$.

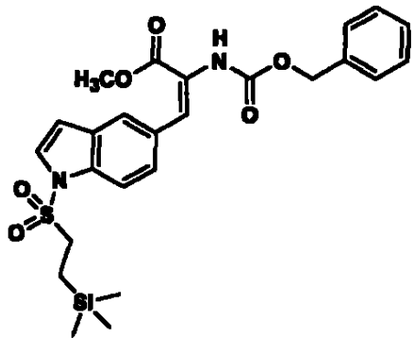
Similarly prepared:

1-(2-Trimethylsilanyl-ethanesulfonyl)-1*H*-indazole-5-carbaldehyde



Mass spec. 311.10 $(MH)^+$.

2-Benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-yl]-acrylic acid methyl ester

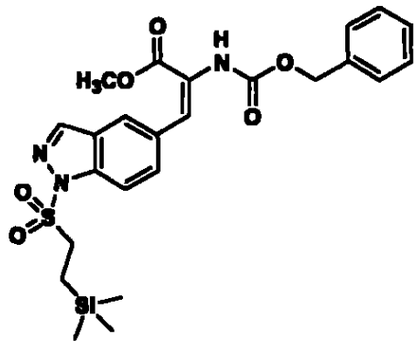


1,1,3,3-Tetramethylguanidine (0.68 mL, 5.43 mmol) was added at room temperature to a solution of N-(benzyloxycarbonyl)-α-phophonoglycine trimethyl ester (1.88g, 5.69 mmol) in tetrahydrofuran (40 mL). The mixture was stirred at room temperature for 15 min and cooled to –78°C, and a solution of 1-(2-

trimethylsilanyl-ethanesulfonyl)-1*H*-indole-5-carbaldehyde (1.6g, 5.17 mmol) in tetrahydrofuran (15 mL) was added slowly. The resulting reaction mixture was stirred at –78°C for 2h and then warmed to room temperature in 3h. Solvents were removed *in vacuo* and the residue was subjected to flash chromatography on silica gel using methylene chloride/hexanes (1:1.5) with 1% triethylamine as eluent to afford the title compound as a 92:8 *Z/E* mixture (determined by integration of CO_2CH_3, for Z isomer at 3.79 ppm, and E isomer at 3.65 ppm). For the Z isomer: ^{1}H-NMR (CD_3CN, 500 MHz) δ 7.96 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 3.7 Hz, 1H), 7.51 (s, 1H), 7.43 – 7.35 (m, 5H), 7.67 (d, J = 3.7 Hz, 1H), 5.16 (s, 2H), 3.79 (s, 3H), 3.42 – 3.38 (m, 2H), 0.87 – 0.83 (m, 2H), -0.04 (s, 9H). Mass spec. 515.20 $(MH)^+$.

Similarly prepared:

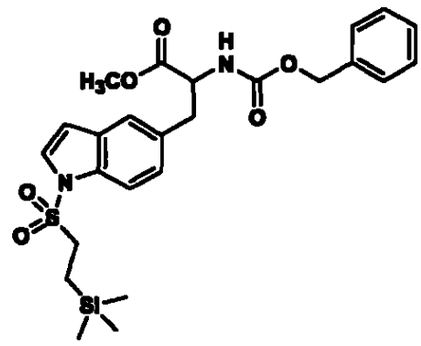
2-Benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-acrylic acid methyl ester



Flash chromatography on silica gel using methylene chloride containing 1% triethylamine as eluent afforded the title compound as a 95:5 Z/E mixture (determined by the integration of –CH=C(CO_2Me)(NHCBz), 3.72g, 92%). For the Z isomer: ^{1}H-NMR (CD_3CN, 500 MHz) δ 8.39 (s, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.84 (dd, J = 8.8, 1.2 Hz, 1H), 7.51 (s, 1H), 7.43 – 7.35 (m, 5H), 5.14 (s, 2H), 3.81 (s, 3H), 3.51 – 3.47 (m, 2H), 0.83 – 0.79 (m, 2H), -0.02 (s, 9H). Mass spec. 516.18 $(MH)^+$.

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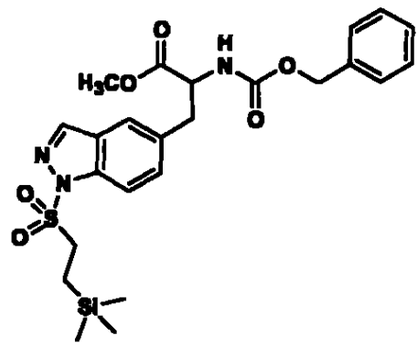
(±)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-propionic acid methyl ester



To a flame dried 500 mL of round bottom flask was added 2-benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-acrylic acid methyl ester (2.24h, 4.36 mmol), methanol (100 mL) and 10% palladium on charcoal (0.52g). The mixture was degassed and purged with hydrogen five times. It was stirred at room temperature for 1h and filtered through a pad of celite. Solvents were removed and the residue was subjected to flash chromatography using ethyl acetate/hexanes (1:1 and 2:1) containing 1% triethylamine to afford the tile compound as a colorless viscous liquid (1.27g, 76%), which solidified upon cooling. ^{1}H-NMR (CD_3CN, 500 MHz) δ 7.82 (d, J = 8.2 Hz, 1H), 7.51 – 7.49 (m, 2H), 7.22 (dd, J = 8.6, 1.5 Hz, 1H), 6.72 (d, J = 3.7 Hz, 1H), 3.70 (dd, J = 7.3, 6.1 Hz, 1H), 3.65 (s, 3H), 3.38 – 3.34 (m, 2H), 3.08 (dd, J = 13.4, 5.8 Hz, 1H), 2.95 (dd, J = 13.4, 7.3 Hz, 1H), 0.82 – 0.79 (m, 2H), -0.05 (s, 9H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 176.0, 134.4, 133.4, 131.1, 127.9, 126.4, 122.4, 113.1, 107.7, 56.6, 51.7, 50.8, 41.3, 10.1, -2.7. Mass spec. 383.16 $(MH)^+$.

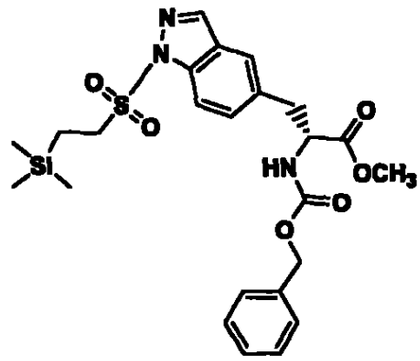
Similarly prepared:

(±)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



^{1}H-NMR (CD_3CN, 500 MHz) δ 8.34 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.46 (dd, J = 8.6, 1.5 Hz, 1H), 3.71 (dd, J = 7.3, 5.8 Hz, 1H), 3.65 (s, 3H), 3.48 – 3.44 (m, 2H), 3.12 (dd, J = 13.7, 5.8 Hz, 1H), 2.97 (dd, J = 13.7, 7.6 Hz, 1H), 0.83 – 0.79 (m, 2H), -0.02 (s, 9H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 175.9, 141.1, 140.5, 134.6, 131.5, 126.0, 122.2, 112.7, 56.4, 51.8, 51.1, 40.9, 9.8, -2.6. Mass spec. 384.15 $(MH)^+$.

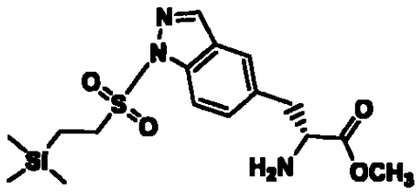
(*R*)-2-Benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



In a glove bag that was subjected to 3 vacuum/nitrogen purge cycles, an AIRFREE® (Schlenk) reaction flask equipped with stir bar was charged with (-)-1,2-bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium (I) trifluoromethylsulfonate (123 mg, 0.17 mmol, 5 mol%), sealed with a rubber septum, and removed from the glove bag. The 2-benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-acrylic acid methyl ester (1.75 g, 3.40 mmol) was weighed into a second AIRFREE® (Schlenk) reaction flask equipped with stir bar and sealed with a rubber septum. After 3 vacuum/nitrogen purge cycles, it was dissolved in a mixture of anhydrous methanol (75 mL) and anhydrous

methylene chloride (15 mL). Both solvents were deoxygenated prior to addition by sparging with nitrogen for at least 1 h. Once in solution, the mixture was again subjected to 3 vacuum/nitrogen purge cycles. The dehydroamino acid solution was introduced into the AIRFREE® (Schlenk) reaction flask containing the catalyst via cannula. The reaction mixture was subjected to 5 vacuum/hyrogen purge cycles before opening the flask to 1 atm. of hydrogen (balloon). After 16 h, the reaction mixture was purged with 3 vacuum/nitrogen purge cycles . The solvent was evaporated and the residue was subjected to column chromatography (gradient 1:4 ethyl acetate/hexanes to 1:2 ethyl acetate/hexanes) to give 1.5 g (85%) of the title compound as a white solid with 98.4% ee as determined by HPLC analysis using a Chirocel OD column with 80% hexane/20% ethanol as eluent (retention times: 13.9 min for title compound and 11.2 min for *S*-enantiomer). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.17 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.35-7.25 (m, 6H), 5.29-5.24 (m, 1H), 5.08 (dd, J = 19.0, 12.1 Hz, 2H), 4.73-4.67 (m, 1H), 3.73 (s, 3H), 3.38-3.32 (m, 2H), 3.29 (dd, J = 14.2, 5.6 Hz, 1H), 3.19 (dd, J = 13.9, 5.6 Hz, 1H), 0.91-0.85 (m, 2H), -0.02 (s, 9H). Mass spec.: 518 $(MH)^+$.

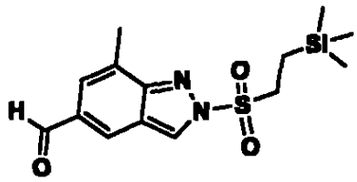
(*R*)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



A mixture of (*R*)-2-Benzyloxycarbonylamino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester (1.24 g, 2.40 mmol) and 10% palladium on carbon (124 mg) in methanol (50 mL) was agitated for 2 h under 50 psi hydrogen using a Parr hydrogenator. The reaction mixture was purged with 3 vacuum/nitrogen purge cycles. The reaction mixture was then filtered through a pad of celite and the pad was rinsed with several portions of methanol. The methanol filtrate was evaporated to give 879 mg (96%) of the title compound as a sticky gum. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H), 3.38-3.32 (m, 2H), 3.21 (dd, J =

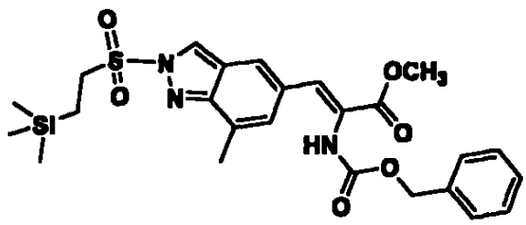
13.9, 5.1 Hz, 1H), 2.98 (dd, J = 13.9, 7.9 Hz, 1H), 0.91-0.85 (m, 2H), -0.02 (s, 9H). Mass spec.: 384 $(MH)^+$

7-Methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazole-5-carbaldehyde



To a suspension of 7-methylindazole 5-aldehyde (3.0 g, 18.7 mmol) in methylene chloride (150 mL) was added triethylamine (7.83 mL, 56.2 mL, 3 equiv) followed by dropwise addition of neat 2-trimethylsilanyl-ethanesulfonyl chloride (5.60 g, 28.1 mmol, 1.5 equiv). The mixture gradually became homogeneous and was allowed to stir at room temperature for 16 h. The solution was concentrated to a minimum amount of methylene chloride and then subjected to flash column chromatography on silica gel (1:4 ethyl acetate/hexanes) to give 4.7 g (77%) of the product as a pale yellow solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.98 (s, 1H), 8.77 (s, 1H), 8.09 (s, 1H), 7.64 (s, 1H), 3.64-3.58 (m, 2H), 2.65 (s, 3H), 0.88-0.82 (m, 2H), 0.01 (s, 9H).

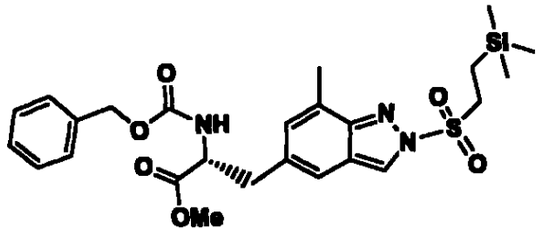
2-Benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-acrylic acid methyl ester



To a solution of N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (4.93 g, 14.9 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (75 mL) was added tetramethylguanidine (1.78 mL, 1.05 equiv). The mixture was stirred at room temperature under nitrogen for 5 min and was then cooled to -78°C. After stirring for 15 min at -78°C, a solution of 7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazole-5-carbaldehyde in tetrahydrofuran (25 mL) was added. The reaction mixture was allowed to slowly warm to room temperature overnight. Although the

reaction was incomplete, the solvent was evaporated. The resulting residue was dissolved in ethyl acetate and washed with 1M sulfuric acid. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated. Flash column chromatography (1:4 ethyl acetate/hexanes) gave 2.66 g (37 %) of the product as white glass foam. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.62 (s, 1H), 7.38-7.25 (m, 7H), 6.48 (bs, 1H), 5.10 (s, 2H), 3.83 (s, 3H), 3.58-3.52 (m, 2H), 2.51 (s, 3H), 0.89-0.83 (m, 2H), 0.02 (s, 9H). Mass spec.: 530 $(MH)^+$.

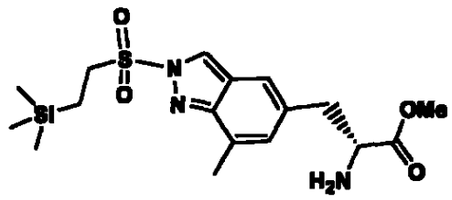
(*R*)-2-Benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-propionic acid methyl ester



In a glove bag that was subjected to 3 vacuum/nitrogen purge cycles, an AIRFREE® (Schlenk) reaction flask equipped with stir bar was charged with (-)-1,2-bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium (I) trifluoromethylsulfonate (259 mg, 0.36 mmol, 9 mol-%), sealed with a rubber septum, and removed from the glove bag. The 2-benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-acrylic acid methyl ester (2.03 g, 3.83 mmol) was weighed into a second AIRFREE® (Schlenk) reaction flask equipped with stir bar and sealed with a rubber septum. After 3 vacuum/nitrogen purge cycles, it was dissolved in anhydrous methanol (80 mL, deoxygenated prior to addition by sparging with nitrogen for at least 1 h). Once in solution, it was again subjected to 3 vacuum/nitrogen purge cycles. The dehydroamino acid solution was transferred via cannula to the AIRFREE® (Schlenk) reaction flask containing the catalyst. The reaction mixture was purged with 5 vacuum/hydrogen purge cycles before opening the flask to a balloon of hydrogen (1 atm). After 2.5 h, the reaction mixture was purged with 3 vacuum/nitrogen purge. cycles. The solvent was evaporated and the residue was subjected to column chromatography (gradient 1:4 ethyl acetate/hexanes to 1:2 ethyl acetate/hexanes) to

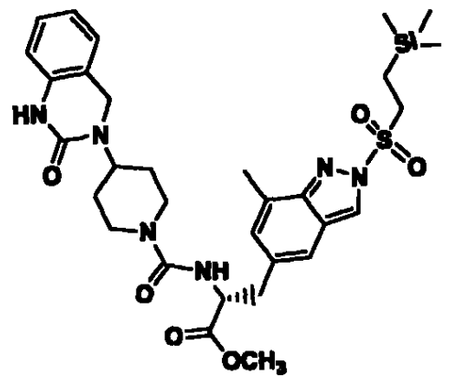
give 1.4 g (68%; ee = 99.2%) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 7.34 (s, 5H), 7.19 (s, 1H), 6.87 (s, 1H), 5.24 (d, J = 8.1 Hz, 1H), 5.08 (dd, J = 18.3, 12.1 Hz, 2H), 4.67 (dd, J = 13.9, 6.2 Hz, 1H), 3.73 (s, 3H), 3.57 –3.51 (m, 2H), 3.16 (dd, J = 14.0, 5.9 Hz, 1H). 3.06 (dd, J = 13.9, 6.6 Hz, 1H), 2.55 (s, 3H), 0.89-0.83 (m, 2H), 0.01 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.0, 155.7, 151.7, 136.2, 132.2, 129.8, 129.5, 128.6, 128.4, 128.2, 125.1, 121.1, 118.1, 67.1, 54.7, 52.5, 51.1, 38.6, 17.1, 9.7, -2.0. Mass spec.: 532 $(MH)^+$.

(*R*)-2-Amino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-propionic acid methyl ester



2-Benzyloxycarbonylamino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-propionic acid methyl ester, (1.35 g, 2.54 mmol) and 10% palladium on carbon (135 mg) in methanol (40 mL) were agitated for 3.0 h under 55 psi hydrogen using a Parr apparatus. The reaction mixture was purged with 3 vacuum/nitrogen purge cycles. The reaction mixture was then filtered through a pad of celite and the pad was rinsed with several portions of methanol. The methanol filtrate was evaporated to give the title compound (1.01 g, quantitative yield) as a sticky gum. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.29 (s, 1H), 6.97 (s, 1H), 3.79-3.73 (m, 1H), 3.73 (s, 3H), 3.56-3.50 (m, 2H), 5.12 (dd, J = 13.5, 5.12 Hz, 1H), 4.85 (dd, J = 13.5, 8.1 Hz, 1H), 2.58 (s, 3H), 0.87-0.81 (m, 2H), 0.01 (s, 9H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 175.5, 151.8, 133.7, 129.9, 129.4, 125.0, 121.3, 117.9, 55.5, 52.1, 51.1, 41.4, 17.1, 9.8, -2.1. Mass spec.: 398 $(MH)^+$.

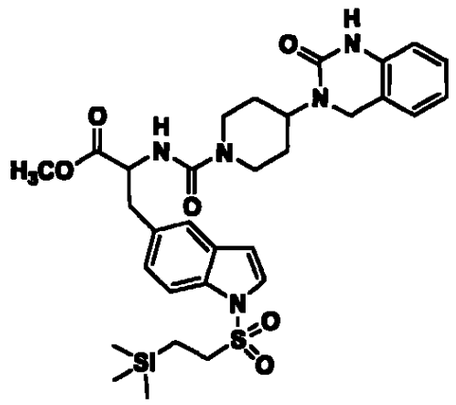
(*R*)-3-[7-Methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-2*H*-indazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A mixture of 2-amino-3-[7-methyl-2-(2-trimethylsilanyl-ethanesulfonyl)-*2H*-indazol-5-yl]-propionic acid methyl ester (500 mg, 1.26 mmol), *N,N*-diisopropylethylamine (0.66 mL, 3.77 mmol) and disuccinimidylcarbonate (322 mg, 1.26 mmol) were stirred together in methylene chloride (20 mL) for 30 min at room temperature. Then, 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one (444 mg, 1.35 mmol) was added and the reaction mixture was allowed to stir overnight at room temperature. The solvent was evaporated and the residue was subjected to flash column chromatography (1:4 acetone/ethyl acetate) to give 490 mg (60 % yield) of the title compound as a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.23 (s, 1H), 7.19-7.14 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.97-6.93 (m, 2H), 6.77 (s, 1H), 6.65 (d, J = 7.7 Hz, 1H), 4.99 (d, J = 7.3 Hz, 1H), 4.81 (dd, J = 13.5, 6.2 Hz, 1H), 4.58-4.46 (m, 1H), 4.27 (s, 2H), 4.10-3.98 (m, 2H), 3.73 (s, 2H), 3.57-3.51 (m, 2H), 3.14-3.11 (m, 2H), 2.95-2.83 (m, 2H), 2.58 (s, 3H), 1.77-1.65 (m, 4H), 0.92-0.84 (m, 2H), -0.01 (s, 9H). Mass spec.: 655 $(MH)^+$.

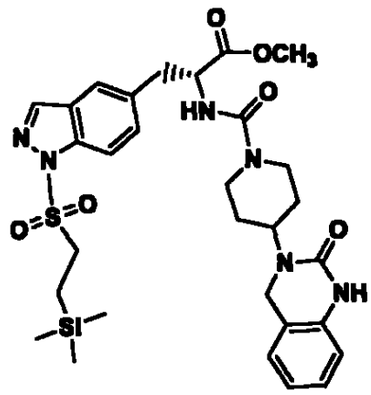
Similarly prepared:

(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-yl]-propionic acid methyl ester



^{1}H-NMR (CD_3OD, 500 MHz) δ 7.85 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.27 (dd, J = 8.6, 1.5 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz,1H), 6.95 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 3.7 Hz, 1H), 4.44 – 4.38 (m, 1H), 4.26 (s, 2H), 4.13 – 4.08 (m, 2H), 3.73 (s, 3H), 3.34 – 3.29 (m, 4H), 3.13 (dd, J = 13.5, 9.4 Hz, 1H), 2.89 – 2.79 (m, 2H), 1.76 –1.70 (m, 1H), 1.63 – 1.59 (m, 3H), 0.76 – 0.72 (m, 2H), -0.07 (s, 9H); Mass spec.: 640.40 $(MH)^+$.

(*R*)-2-{[4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester

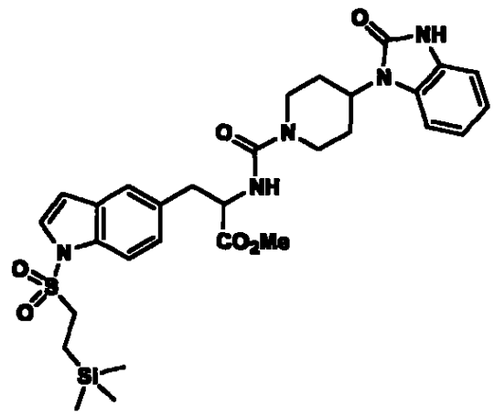


A solution of (*R*)-2-Amino-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester (764 mg, 1.99 mmol), *N,N*-diisopropylethylamine (1.10 mL, 5.97 mmol) and disuccinimidylcarbonate (509 mg, 1.99 mmol) in methylene chloride (20 mL) was stirred for 40 min at room temperature. Then, 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one (70% pure, 703 mg, 2.13 mmol) was added and the reaction mixture was allowed to stir overnight at room temperature. The solvent was evaporated *in vacuo* and the residue

was subjected to flash column chromatography (1:4 acetone/ethyl acetate) to give 1.15 g (90 %) of the title compound. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H)l, 6.76 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 5.01 (d, J = 7.6 Hz, 1H), 4.84 (dd, J = 13.1, 6.0 Hz, 1H), 4.56-4.49 (m, 1H), 4.28 (s, 2H), 4.13-3.98 (m, 2H), 3.73 (s, 3H), 3.39-3.35 (m, 2H), 3.28 (dd, J = 14.0, 6.1 Hz, 1H), 3.24 (dd, J = 13.7, 5.8 Hz, 1H), 2.94-2.87 (m, 2H), 1.75-1.67 (m, 4H), 0.91-0.87 (m, 2H), -0.02 (s, 9H). Mass spec.: 641 $(MH)^+$.

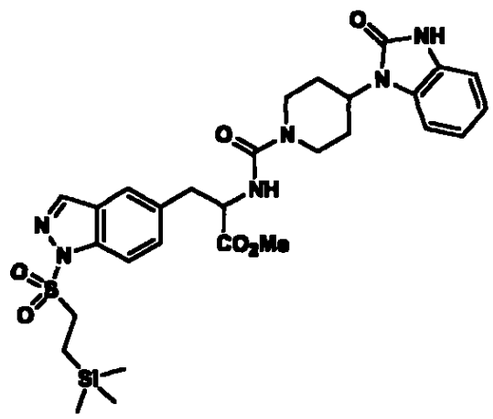
Similarly prepared:

(±)-2-{[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-propionic acid methyl ester



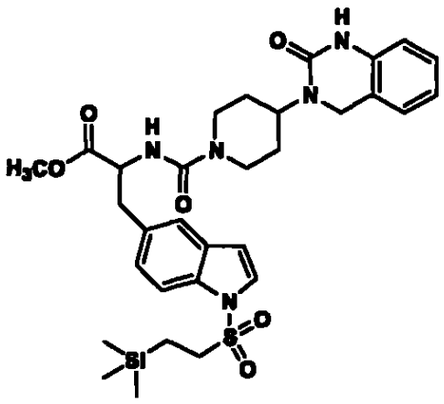
^{1}H-NMR (CD_3CN, 500 MHz) δ 9.78 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 3.7 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 7.10 – 7.08 (m, 1H), 7.05 – 7.03 (m, 1H), 6.99 – 6.97 (m, 2H), 6.70 (d, J = 3.7 Hz, 1H), 5.91 (d J = 7.9 Hz, 1H), 4.66 (q, J = 8.2 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.14 (br s, 1h), 3.68 (s, 3H), 3.36 – 3.32 (m, 2H), 3.27 (dd, J = 14.0, 5.5 Hz, 1H), 3.18 (dd, J = 13.7, 8.5 Hz, 1H), 2.90 – 2.84 (m, 2H), 2.55 (br s, 1H), 2.36 – 2.21 (m, 2H), 1.74 – 1.70 (m, 2H), 0.82 – 0.78 (m, 2H), -0.09 (s, 9H). Mass spec. 626.26 $(MH)^+$.

(±)-2-{[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester



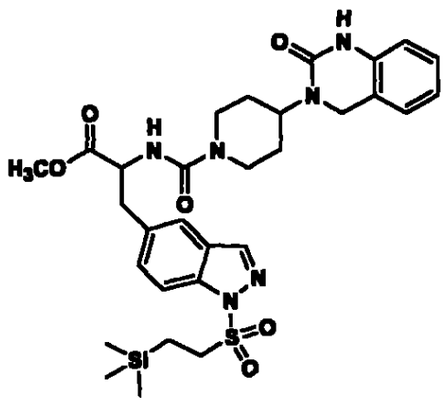
^{1}H-NMR (CD_3CN, 500 MHz) δ 9.61 (br s, 1H), 8.35 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.51 (dd, J = 8.8, 1.5 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.05 – 7.02 (m, 1H), 7.00 – 6.97 (m, 2H), 5.90n(d, J = 7.9 Hz, 1H), 4.67 4.62 (m, 1H), 4.42 –4.36 (m, 1H), 4.13 – 4.07 (br s, 1H), 3.68 (s, 3H), 3.45 – 3.42 (m, 2H), 3.30 (dd, J = 14.0, 5.8 Hz, 1H), 3.20 (dd, J = 13.7, 8.8Hz, 1H), 2.89 – 2.84 (m, 2H), 2.52 (br s, 1H), 2.33-2.23 (m, 2H), 1.72 – 1.69 (m, 2H), 0.80 – 0.76 (m, 2H), -0.07 (s, 9H). Mass spec. 627.25 $(MH)^+$.

(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-yl]-propionic acid methyl ester



^{1}H-NMR (CD_3OD, 500 MHz) δ 7.85 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.27 (dd, J = 8.6, 1.5 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz,1H), 6.95 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 3.7 Hz, 1H), 4.44 – 4.38 (m, 1H), 4.26 (s, 2H), 4.13 – 4.08 (m, 2H), 3.73 (s, 3H), 3.34 – 3.29 (m, 4H), 3.13 (dd, J = 13.5, 9.4 Hz, 1H), 2.89 – 2.79 (m, 2H), 1.76 –1.70 (m, 1H), 1.63 – 1.59 (m, 3H), 0.76 – 0.72 (m, 2H), -0.07 (s, 9H). Mass spec. 640.40 $(MH)^+$.

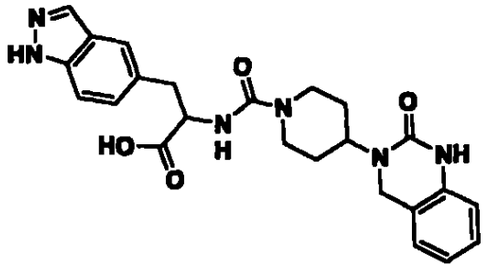
(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-yl]-propionic acid methyl ester



^{1}H-NMR (CD_3OD, 500 MHz) δ 8.39 (d, J = 0.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.75 (s, 1H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.94 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 4.63 – 4.60 (m, 1h), 4.43 – 4.37 (m, 1H), 4.27 (s, 2H), 4.11 (br s, 1H), 4.08 (br s, 1H), 3.71 (s, 3H), 3.47 – 3.43 (m, 2H), 3.37 – 3.33 (m, 1H), 3.18 (dd, *j* = 13.5, 10.0 Hz, 1H), 2.87 – 2.79 (m, 2H), 1.73 – 1.59 (m, 4H), 0.80 – 0.75 (m, 2H), -0.05 (s, 9H);^{13}C-NMR (CD_3OD, 125 MHz) δ 173.7, 155.5, 158.1, 141.0, 140.6, 137.2, 134.4, 131.3, 128.2, 126.1, 125.8, 122.2, 121.9, 118.3, 113.4, 112.6, 55.9, 52.1, 51.7, 50.8, 48.9, 48.6, 48.4, 48.2, 48.0, 47.9, 47.7, 47.5, 43.8, 43.7, 43.1, 37.2, 28.5, 9.8, -3.2. Mass spec.: 641.40 $(MH)^+$.

Example 1

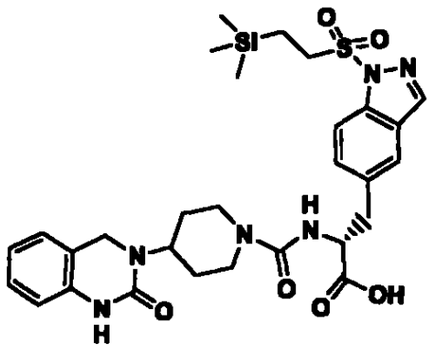
(±)-3-(1*H*-Indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



A solution of 5-(2-methoxycarbonyl-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-ethyl)-indazole-1-carboxylic acid

tert-butyl ester (168 mg, 0.29 mmol) was dissolved in tetrahydrofuran (5 mL) and methanol (5 mL) was cooled to 0°C. A solution of lithium hydroxide monohydrate (49 mg, 2.04 mmol) in water (5 mL) was added. The reaction mixture was stirred at 0°C for 6 h and then placed in the freezer for a further 16 h. The solvents were removed *in vacuo* and the residue dissolved in water (15 mL). The pH of the aqueous solution was adjusted to ca. 1 with 1N hydrochloric acid. The resulting white solid precipitated was collected by filtration. The solid was dried under vacuum to give the title compound (108 mg, 80%). ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 12.94 (bs, 1H), 9.19 (s, 1H), 8.01 (s, 1H), 7.61 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.5 , 1.5 Hz, 1H), 7.13-7.06 (m, 2H), 6.86 (t, J = 7.0 Hz, 1H), 6.76-6.72 (m, 2H), 4.32-4.24 (m, 2H), 4.09-4.02 (m, 4H), 3.17-2.97 (m, 2H), 2.72-2.59 (m, 2H), 1.57-1.35 (m, 4H). IR (KBr, cm^{-1}) 3424, 2963, 2930, 1660, 1628, 1505, 1474, 1446, 753. Mass spec.: 463 $(MH)^+$.

(*R*)-2-{[4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid

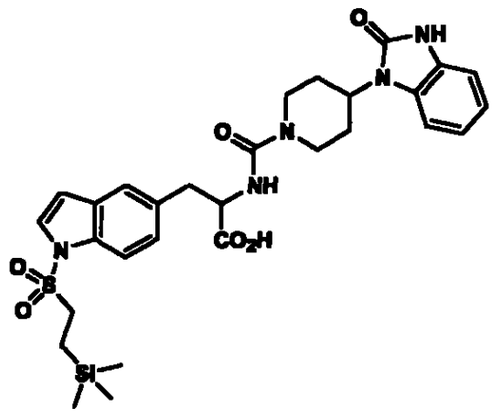


A solution of (*R*)-2-{[4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester (775 mg, 1.21 mmol) in tetrahydrofuran (9 mL) and methanol (3 mL) was cooled to 0°C. A solution of lithium hydroxide monohydrate (115 mg, 4.84 mmol) in water (3 mL) was added. The reaction mixture was stirred at 0°C for 2 h and then placed in the freezer at -15°C for 16 h. While cooling the reaction mixture with an ice bath, the pH was increased to ca. 7 by addition of 1N hydrochloric acid (3.8 mL). Organic solvents were removed under vacuum. The resulting aqueous solution was extracted with ethyl acetate after additon of more 1N

hydrochloric acid (0.5 mL). The combined extracts were dried over magnesium sulfate, filtered and evaporated to give 684 mg (90%) of the title compound as a white solid. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 9.21 (s, 1H), 8.58 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.13-7.09 (m, 2H), 6.88-6.83 (m, 1H), 6.76-6.74 (m, 2H), 4.33-4.27 (m, 2H), 4.18 (s, 2H), 4.09-3.96 (m, 3H), 3.57-3.51 (m, 2H), 3.25-3.04 (m, 2H), 2.74-2.60 (m, 2H), 1.54-1.43 (m, 4H), 0.70-0.64 (m, 2H), -0.08 (s, 9H). Mass spec.: 627 $(MH)^+$.

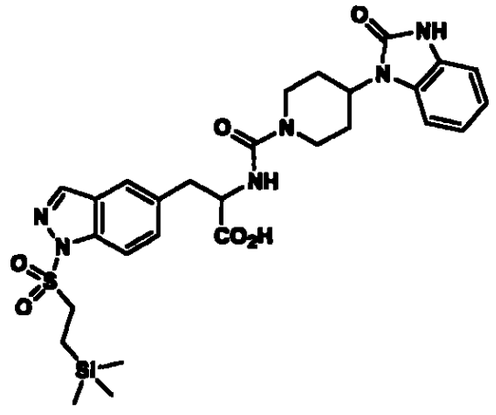
Similarly prepared:

(±)-2-{[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-yl]-propionic acid



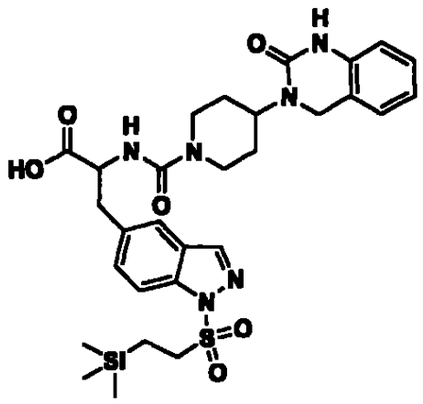
Mass spec. 612.25 $(MH)^+$.

(±)-2-{[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid



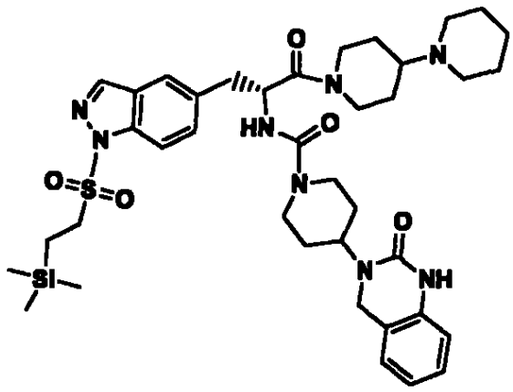
Mass spec. 613.26 $(MH)^+$.

(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-yl]-propionic acid



^{1}H-NMR (CD_3CN, 500 MHz) δ 8.37 (s, 1H), 8.08 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.53 (dd, J = 8.5, 1.5 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.98 (td, j = 7.6, 1.2 Hz, 1H), 6.79 (d, j = 8.0 Hz, 1H), 6.28 (br s, 3H), 4.54 – 4.49 (m, 1H), 4.37 – 4.32 (m, 1H), 4.30 (s, 2H), 3.98 – 3.92 (m, 2H), 3.45 – 3.41 (m, 2H), 3.37 (dd, j = 14.0, 4.9 Hz, 1H), 3.20 (dd, J = 14.0, 9.7 Hz, 1H), 2.84 – 2.77 (m, 2H), 1.65 – 1.57 (m, 4H), 0.79 – 0.76 (m, 2H), -0.05 (s, 9H). Mass spec.: 627.30 $(MH)^+$.

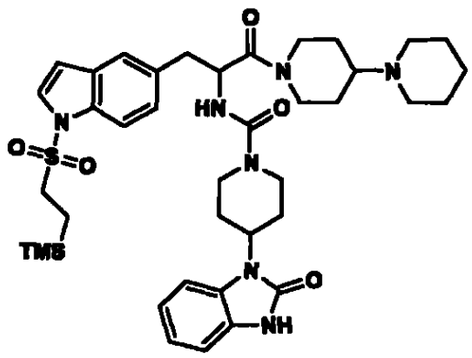
(*R*)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide



To a solution of (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid (554 mg, 0.88 mmol) and *N,N*-diisopropylethylamine (0.62 mL, 3.54 mmol) in methylene chloride (20 mL) was added a solution of 4-piperidinopiperidine (164 mg, 0.97 mmol) and PyBOP® (460 mg, 0.88 mmol) in methylene chloride (15 mL). The reaction mixture was stirred for 16 h at room temperature. It was then concentrated to approximately 2 mL and subjected to flash column chromatography using methylene chloride/methanol/triethylamine (94:5:1) as eluent to give 599 mg (87%) of the title compound as a white solid. ^{1}H-NMR (CD_3CN, 300 MHz) δ 8.37 (s, 0.5H), 8.36 (s, 0.5H), 8.02-7.96 (m, 1H), 7.74 (s, 0.5H), 7.71 (s, 0.5H), 7.55-7.46 (m, 1H), 7.21-7.12 (m, 2H), 6.97-6.92 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 5.71 (t, J = 8.1 Hz, 1H), 5.00 (dd, J = 15.0, 8.1 Hz, 1H), 4.63-4.51 (m, 1H), 4.39-4.29 (m, 1H), 4.29 (s, 2H), 4.10-3.96 (m, 3H), 3.46-3.40 (m, 2H), 2.92-2.70 (m, 8H), 2.58-2.37 (m, 5H), 1.74-1.40 (m, 13H), 0.80-0.74 (m, 2H), -0.04 (s, 9H). Mass spec.: 778 $(MH)^+$.

Similarly prepared:

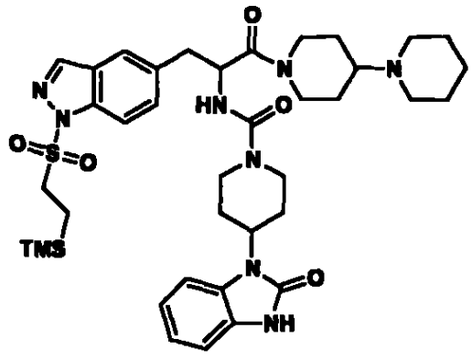
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indol-5-ylmethyl]-ethyl}-amide



^{1}H-NMR (CD_3CN, 500 MHz) δ 9.42 (br s, 1H), 7.80 (d, J = 8.5 Hz, 0.6 H), 7.78 (d, J = 8.2 Hz, 0.4 H), 7.50 (s, 1H), 7.43 (t, J = 3.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 0.6 H), 7.23 (d, J = 8.5 Hz, 0.4 H), 7.10 – 7.07 (m, 1H), 7.02 – 6.95 (m, 3H), 6.69 (s, 0.4 H), 6.68 (s, 0.6 H), 5.88 (d, J = 8.5 Hz, 0.6 H), 5.85 (d, J = 8.4 Hz, 0.4 H), 5.04 – 4.98 (m, 1H), 4.49 (s, 0.4 H), 4.46 (s, 0.6 H), 4.36 – 4.30 (m, 1H), 4.11 – 4.07 (m, 1H),

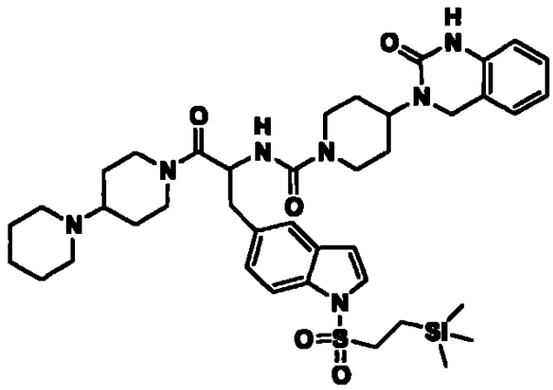
3.97 – 3.91 (m, 1H), 3.31 – 3.28 (m, 2H), 3.11 – 3.05 (m, 6 H), 2.87 – 2.80 (m, 2H), 2.43 – 2.07 (m, 8 H), 1.78 – 1.74 (m, 4H), 1.71 – 1.65 (m, 2H), 1.46 – 1.40 (m, 2H), 1.37 – 1.31 (m, 2H), 0.80 – 74 (m, 2H), -0.10 (s, 9H). LC/MS: t_R = 2.47 min, 762.37 $(MH)^+$.

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide



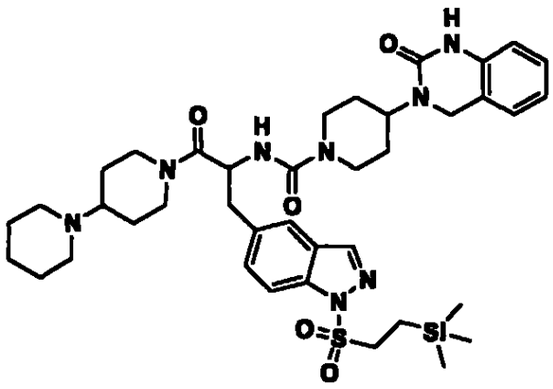
^{1}H-NMR (CD_3CN, 500 MHz) δ 9.67 (s, 1H), 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 0.55 H), 7.93 (d, J = 8.6 Hz, 0.45 H), 7.70 (s, 1H), 7.51 (d, J = 8.6 Hz, 0.55 H), 7.47 (d, J = 8.8 Hz, 0.45 H), 7.08 – 7.05 (m, 1H), 7.03 – 6.99 (m, 1H), 6.98 – 6.94 (m, 2H), 6.01 (d, J = 7.9 Hz, 0.45 H), 5.96 (d, J = 7.9 Hz, 0.55 h), 5.05 – 5.00 (m, 1H), 4.49 – 4.46 (m, 1H), 4.35 – 4.29 (m, 1H), 4.10 – 4.05 (m, 1H), 4.00 – 3.93 (m, 1H), 3.40 – 3.36 (m, 2H), 3.17 – 3.30 (m, 6H), 2.91 – 2.71 (m, 2H), 2.52 – 2.13 (m, 8H), 1.76 9br s, 4H), 1.69 – 1.65 (m, 2H), 1.44 – 1.41 (m, 2H), 1.34 – 1.30 (m, 2H), 0.77 – 0.71 (m, 2H), -0.08 (s, 9H). LC/MS: t_R = 2.35 min, 763.35 $(MH)^+$.

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-ylmethyl]-ethyl}-amide



^{1}H-NMR (CD_3CN, 500 MHz) δ 8.17 (s, 0.6H), 8.16 (s, 0.4H), 7.84 (d, J = 8.5 Hz, 0.6 H), 7.81 (d, J = 8.5 Hz, 0.4 H), 7.54 (s, 0.4 H), 7.53 (s, 0.6H), 7.48 (t, J = 4.1 Hz, 1H), 7.31 (dd, J = 8.5, 1.5 Hz, 0.6 H), 7.28 (dd, J = 8.5, 1.5 Hz, 0.4 H), 7.18 (t, j = 7.4 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.93 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 6.09 (d, J = 8.2 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.53 – 4.50 (m, 1H), 4.40 – 4.34 (m, 1H), 4.26 (s, 1.2H)< 4.24 (s, 0.8H), 3.99 – 3.94 (m, 1H), 3.35 – 3.30 (m, 2H), 3.15 – 3.07 (m, 3H), 3.08 – 3.03 (m, 1H), 2.81 – 2.73 (m, 3H), 2.55 – 2.37 (m, 6H), 2.21 – 2.16 (m, 1H), 2.13 – 2.08 (m, 1H), 1.69 – 1.57 (m, 4H), 1.51 – 1.45 (m, 4H), 1.41 – 1.35 (m, 4H), 0.83 – 0.74 (m, 2H), -0.06 (s, 9H). Mass spec.: 776.44 $(MH)^+$.

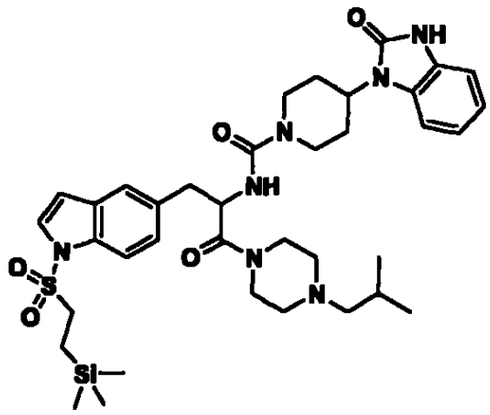
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide



Purified by silica gel chromatography using methylene chloride:methanol/triethylamine (90:10:0.5) as eluent. ^{1}H-NMR (CD_3CN, 500 MHz)

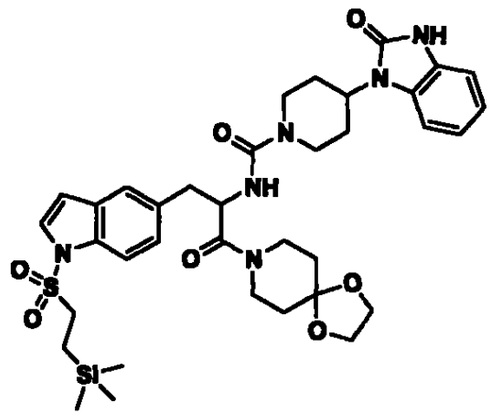
δ 8.36 (s, 1H), 8.04 (s, 1H), 8.01 (d, J = 8.8 Hz, 0.6H), 7.97 (dd, J = 8.8 Hz, 0.4 H), 7.74 (s, 1H), 7.54 (dd, J = 8.5, 1.5 Hz, 0.6 H), 7.51 (dd, J = 8.5, 1.5 Hz, 0.4 H), 7.18 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.05 (d, J = 8.5 Hz, 0.4 H), 6.02 (d, J = 8.5 Hz, 0.6 H), 5.06 – 5.01 (m, 1H), 4.52 – 4.50 (m, 1H), 4.39 – 4.34 (m, 1H), 4.27 (s, 1.2 H), 4.25 (s, 0.8 H), 4.00 – 3.97 (m, 2H), 3.45 – 3.40 (m, 2H), 3.20 – 3.08 (m, 2H), 2.81 – 2.74 (m, 2H), 2.56 – 2.39 (m, 8H), 2.27 – 2.24 (m, 1H), 2.20 – 2.16 (m, 1H), 1.68 – 1.57 (m, 4H), 1.52 – 1.45 (m, 4H), 1.41 – 1.34 (m, 4H), 1.06 – 1.01 (m, 1H), 0.80 –0.75 (m, 2H), -0.07 (s, 9H). Mass spec.: 777.40 $(MH)^+$.

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(4-isobutyl-piperazin-1-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-ylmethyl]-ethyl}-amide



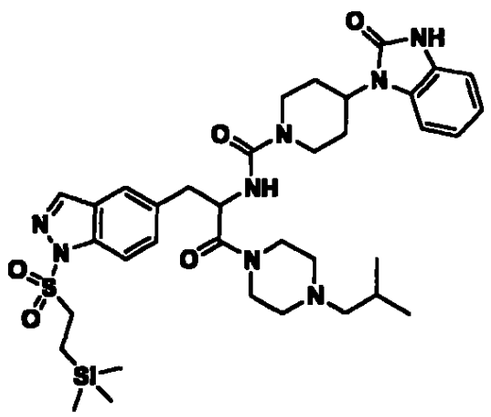
^{1}H-NMR (CD_3CN, 500 MHz) δ 9.75 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.12 - 7.09 (m, 1H), 7.04 – 7.02 (m, 1H), 7.00 – 6.97 (m, 2H), 6.72 (d, J = 3.7 Hz, 1H), 5.97 (d, J = 8.2 Hz, 1H), 5.01 (dd, J = 14.6, 7.2 Hz, 1H), 4.40 – 4.34 (m, 1H), 4.15 – 4.08 (m, 2H), 3.58 – 3.54 (m, 1H), 3.50 – 3.45 (m, 2H), 3.39 – 3.35 (m, 1H), 3.36 – 3.32 (m, 2H), 3.14 – 3.10 (m, 8H), 2.89 – 2.83 (m, 2H), 2.34 – 2.23 (m, 4H), 2.17 – 2.13 (m, 1H), 0.85 (d, J = 6.7 Hz, 6H), 0.83 – 0.80 (m, 2H), -0.06 (s, 9H). Mass spec.: 736.40 $(MH)^+$.

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-ylmethyl]-ethyl}-amide



^{1}H-NMR (CD_3CN, 500 MHz) δ 9.27 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.06 – 7.03 (m, 1H), 7.01 – 6.98 (m, 2H), 6.72 (d, J = 3.6 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 5.05 (dd, J = 15.0, 7.3 Hz, 1H), 4.41 – 4.34 (m, 1H), 4.14 – 4.08 (m, 2H), 3.90 – 3.86 (m, 3H), 3.68 – 3.64 (m, 1H), 3.60 – 3.56 (m, 2H), 3.45 – 3.40 (m, 1H), 3.35 – 3.31 (m, 2H), 3.15 (dd, J = 13.4, 7.1 Hz, 1H), 3.05 (dd, J = 13.4, 7.0 Hz, 1H), 2.89 – 2.83 (m, 2H), 2.34 – 2.19 (m, 3H), 1.73 – 1.70 (m, 2H), 1.64 – 1.56 (m, 2H), 1.53 – 1.49 (m, 1H), 1.29 – 1.26 (m, 1H), 0.84 – 0.80 (m, 2H), -0.05 (s, 9H). Mass spec.: 737.37 $(MH)^+$.

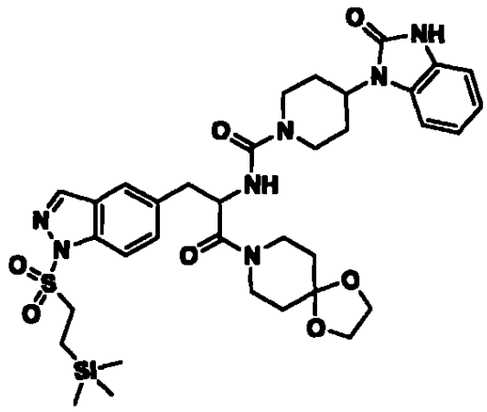
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(4-isobutyl-piperazin-1-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide.



^{1}H-NMR (CD_3CN, 500 MHz) δ 9.84 (s, 1H), 8.37 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J = 8.8, 1.5 Hz, 1H), 7.11 – 7.09 (m, 1H), 7.06 – 7.03 (m, 1H),

7.02 – 6.98 (m, 2H), 5.97 (d, J = 8.2 Hz, 1H), 5.02 (dd,J = 14.3, 7.3 hz, 1H), 4.39 – 4.33 (m, 1H), 4.14 – 4.07 (m, 2H), 3.53 – 3.50 (m, 3H), 3.46 – 3.42 (m, 2H), 3.45 – 3.39 (m, 1H), 3.20 – 3.06 (m, 5H), 2.89 – 2.83 (m, 2H), 2.30 – 2.27 (m, 4H), 2.21 – 2.17 (m, 1H), 1.74 – 1.70 (m, 3H), 0.86 (d, J = 6.7 Hz, 6H), 0.81 – 0.77 (m, 2H), -0.04 (s, 9H). Mass spec.: 737.40 $(MH)^+$.

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid {2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indazol-5-ylmethyl]-ethyl}-amide

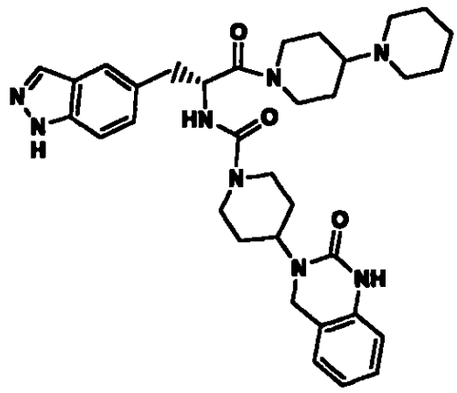


^{1}H-NMR (CD_3CN, 500 MHz) δ 9.34 (s, 1H), 8.36 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.11 – 7.08 (m, 1H), 7.06 – 7.03 (m, 1H), 7.02 – 6.98 (m, 2H), 5.98 (d, J = 8.2 Hz, 1H), 5.06 (dd, J = 14.6, 7.3 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.13 – 4.03 (m, 2H), 3.92 – 3.88 (m, 2H), 3.71 – 3.66 (m, 1H), 3.63 – 3.53 (m, 2H), 3.48 – 3.45 (m, 1H), 3.44 – 3.40 (m, 2H), 3.19 (dd, j = 13.4, 6.5 Hz,1H), 3.08 (dd, J = 13.7, 7.3 Hz, 1H), 2.85 (t, J = 12.8 Hz, 2H), 2.32 – 2.20 (m, 4H), 1.73 – 1.70 (m, 2H), 1.67 – 1.51 (m, 3H), 1.38 – 1.33 (m, 1H), 0.81 – 0.77 (m, 2H), -0.04 (s, 9H). Mass spec.: 738.32 $(MH)^+$.

Example 2

(*R*)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1*H*-indazol-5-ylmethyl)-2-oxo-ethyl]-amide ( )

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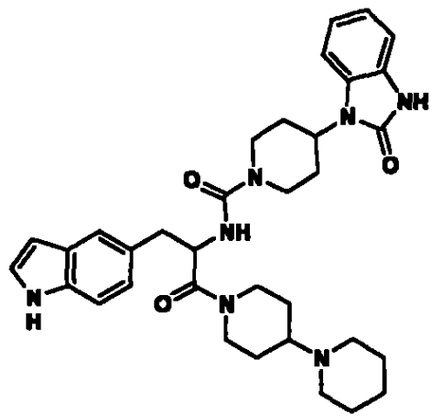


A solution of (*R*)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide (568 mg, 0.73 mmol) and cesium fluoride (1.11 g, 7.31 mmol) was heated at 80°C in acetonitrile (50 mL) for 4.5 h. The reaction mixture was concentrated and the residue was subjected to flash column chromatography (methylene chloride/methanol/triethylamine, 94:5:1) to give 280 mg (63% yield) of the title compound as a white solid with 98.2% ee as determined by HPLC analysis using a Chirocel OD column with 20% B (A = ethanol, B = 0.05% diethylamine in hexanes) as eluent (Retention times: 9.51 min for title compound and 15.9 min for *S*-enantiomer). ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.04 (s, 0.75H), 8.03 (s, 0.25H), 7.67 (s, 0.75H), 7.65 (s, 0.25H), 7.56 (d, J = 8.5 Hz, 0.75H), 7.51 (d, J = 8.5 Hz, 0.25H), 7.41 (d, J = 8.5 Hz, 0.75H), 7.31 (d, J = 8.5 Hz, 0.25H), 7.19-7.12 (m, 2H), 6.97-6.94 (m, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.08-5.05 (m, 1H), 4.60-4.53 (m, 1H), 4.48-4.40 (m, 1H), 4.37 (s, 1.5H), 4.26 (s, 0.5H), 4.24-4.14 (m, 2H), 4.06-3.97 (m, 1H), 3.15 (d, J = 7.9 Hz, 1.5H), 3.12-3.05 (m, 0.5H), 2.94-2.86 (m, 3H), 2.57-2.51 (m, 1.5H), 2.47-2.42 (m, 1H), 2.37-2.33 (m, 0.75H), 2.03-2.02 (m, 1.5H), 1.87-1.75 (m, 3.75H), 1.73-1.68 (m, 2H), 1.67-1.54 (m, 3H), 1.53-1.44 (m, 4H), 1.43-1.34 (m, 2H), 1.30-1.26 (m, 1H), 0.83-0.77 (m, 0.75H), -0.16 to -0.24 (m, 0.75H). Mass spec.: 613 $(MH)^+$.

Similarly prepared:

Example 3

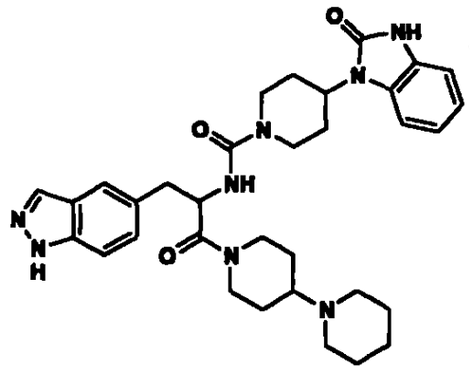
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1*H*-indol-5-ylmethyl)-2-oxo-ethyl]-amide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 10.99 (s, 0.6 H), 10.96 (s, 0.4 H), 10.85 (s, 1H), 7.41 (s, 0.4H), 7.36 (s, 0.6H), 7.33 (d, J = 8.0 Hz, 0.6H), 7.29 – 7.26 (m, 1H), 7.16 – 7.14 (m, 1H), 7.10 (d, J = 7.6 Hz, 0.4 H), 7.02 – 6.96 (m, 4H), 6.81 (br s, 1H), 6.37 – 6.35 (m, 1H), 4.86 (q, J = 8.0 Hz, 0.6 H), 4.80 (q, J = 7.5 Hz, 0.4 H), 4.45 (br s, 1H), 4.38 – 4.32 (m, 1H), 4.21 – 4.16 (m, 1H), 3.98 (br s, 1H), 3.18 (d, J = 5.2 Hz, 0.6H), 3.04 – 2.92 (m, 2.4 H), 2.82 – 2.74 (m, 4H), 2.37 – 2.33 (m, 2H), 2.25 – 2.08 (m, 4H), 2.04 – 1.90 (m, 2H), 1.47 – 1.24 (m, 10H), 0.75 – 0.71 (m, 1H). LC/MS: t_R = 1.90 min, 598.42 $(MH)^+$.

Example 4

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1*H*-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



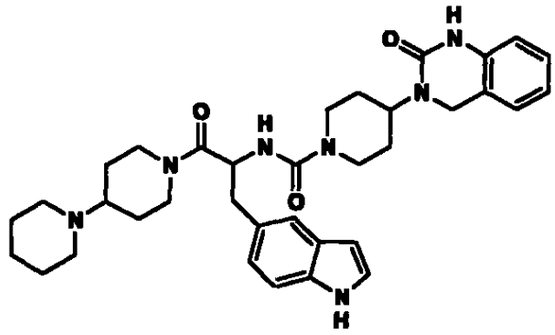
^{1}H-NMR (DMSO-d_6, 500 MHz) δ 10.70 (s, 1H), 8.22 (d, J = 8.2 Hz, 0.6H), 8.11 (s, 0.4H), 8.00 (s, 0.6H), 7.89 (d, J = 9.1 Hz, 0.4 H), 7.62 – 7.57 (m, 1H), 7.50 – 7.43 (m, 1H), 7.30 – 7.26 (m, 1H), 7.14 – 7.08 (m, 1H), 6.99 – 6.95 (m, 2H), 6.85 (br s, 1H), 4.89 – 4.80 (m, 1H), 4.45 – 4.31 (m, 2H), 4.18 – 4.00 (m, 2H), 3.26 – 3.16 (m, 1H),

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3.09 – 2.96 (m, 2H), 2.82 – 2.73 (m, 4H), 2.38 – 2.34 (m, 2H), 2.24 – 2.08 (m, 4H), 2.03 – 1.88 (m, 2H), 1.47 – 1.22 (m, 10H), 0.90 – 0.84 (m, 1H). LC/MS: t_R = 1.73 min, 599.32 $(MH)^+$.

Example 5

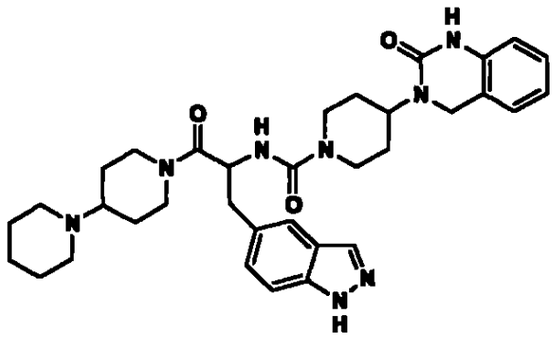
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1H-indol-5-ylmethyl)-2-oxo-ethyl]-amide



A mixture of 4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1H-indol-5-ylmethyl]-ethyl}-amide (52 mg, 0.067 mmol), cesium fluoride (51 mg, 0.33 mmol) in acetonitrile (5 mL) was heated at 80°C for 4h. The solvents were removed *in vacuo* and the residue was subjected to chromatography on silica gel using methylene chloride/methanol/triethylamine (93:5:2) as eluent to afford the title compound as a white solid (70% yield). ^{1}H-NMR (CD_3CN, 500 MHz) δ 9.30 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.39 (d, J = 8.2 Hz, 0.6H), 7.36 (d, J = 8.2 Hz, 0.4 H), 7.24 – 7.21 (m, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.12 – 7.09 (m, 1H), 7.06 (d, J = 8.2 Hz, 0.6 H), 7.02 (d, J = 8.2 Hz, 0.4 H), 6.95 (t, J = 7.4 Hz, 1, 4.04 – 3.93 (m, 1H), 3.07 – 3.02 (m, 1.6H), 2.95 (dd, J = 13.7, 7.1 Hz, 0.4 H), 2.85 – 2.72 (m, 3H), 2.56 – 2.37 (m, 3H), 2.42 – 2.37 (m, 1H), 1.99 – 1.95 (m, 7H), 1.76 – 1.51 (m, 8H), 1.45 – 1.40 (m, 3H). LC/MS: t_R = 1.91 min, 612.44 $(MH)^+$.

Example 6

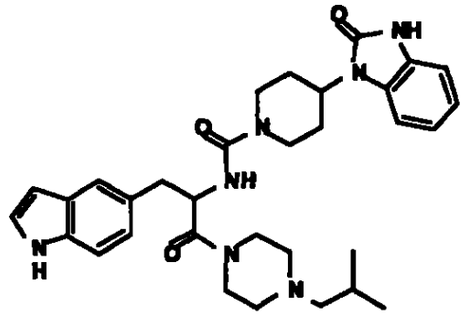
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



Purified by silica gel chromatography using methylene chloride:methanol:triethylamine (93:5:2) as eluent to afford the title compound as a white solid (90% yield). ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.04 (s, 0.7 H), 8.02 (s, 0.3 H), 7.67 (s, 0.7 H), 7.65 (s, 0.3H), 7.56 (d, J = 8.5 Hz, 0.7 H), 7.51 (d, J = 8.5 Hz, 0.3 H), 7.40 (d, J = 8.5 Hz, 0.7 H), 7.33 (d, J = 8.5 Hz, 0.3 H), 7.19 – 7.12 (m, 2H), 6.97 – 6.94 (m, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.08 – 5.05 (m, 1H), 4.59 – 4.54 (m, 1H), 4.48 – 4.42 (m, 1H), 4.37 (s, 1H), 4.27 – 4.20 (m, 2H), 4.04 (d, J = 13.4 Hz, 0.3 H), 3.99 (d, J = 13.4 Hz, 0.7 H), 3.19 – 3.08 (m, 2H), 2.94 – 2.86 (m, 3H), 2.57 (br s, 2H), 2.51 – 2.36 (m, 2H), 2.07 – 2.05 (m 1H), 1.90 –1.31 (m, 16 H). *LC/MS*: t_R = 1.85 min, 613.44 $(MH)^+$. The (R)-enantiomer, whose discrete synthesis is described above (Example 1), was obtained by chiral separation of the racemate by employing the following conditions: Chiracel OD prep column, 50 × 500 mm, 20 um; A = EtOH, B= 0.05%diethylamine/hexane; 20%B @ 65 ml/min for 45 min; retention times: 20.5 min for R and 32.8 min for S enantiomers.

Example 7

(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [1-(1H-indol-5-ylmethyl)-2-(4-isobutyl-piperazin-1-yl)-2-oxo-ethyl]-amide

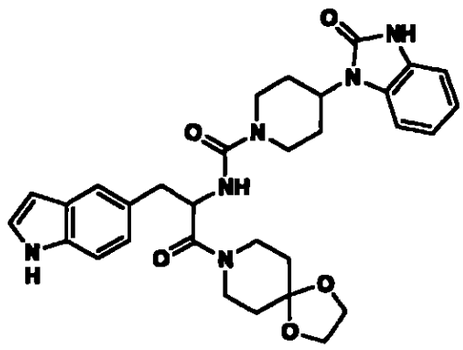


LC/MS: t_R = 2.05 min, 572.31 $(MH)^+$.

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Example 8

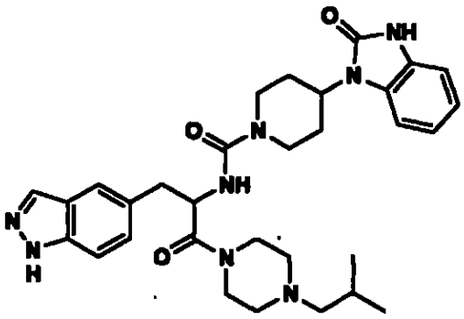
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1H-indol-5-ylmethyl)-2-oxo-ethyl]-amide



LC/MS: $t_R = 2.35$ min, 573.26 $(MH)^+$.

Example 9

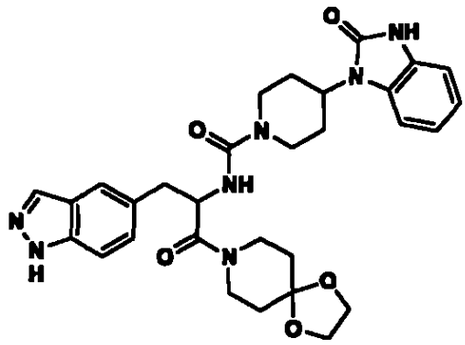
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-(4-isobutyl-piperazin-1-yl)-2-oxo-ethyl]-amide



LC/MS: $t_R = 1.86$ min, 573.28 $(MH)^+$.

Example 10

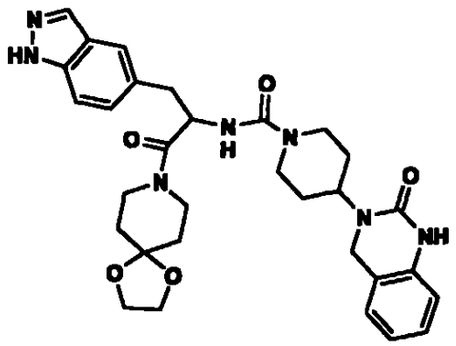
(±)-4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



LC/MS: $t_R = 2.18$ min, 574.23 $(MH)^+$.

Example 11

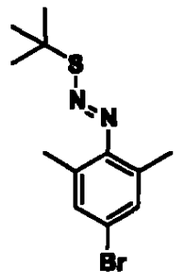
(±)-4-(2-Oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-1-(1*H*-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



To a solution of the 3-(1*H*-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (95 mg, 0.21 mmol) and *N,N*-diisopropylethylamine (0.14 mL, 0.82 mmol) in dimethylformamide (5 mL) was added a solution of 1,4-dioxa-8-azaspiro[4,5]decane (32 mg, 0.23 mmol) and PyBOP® (107 mg, 0.21 mmol) in methylene chloride (5 mL). The reaction mixture was stirred for 16 h at room temperature. All solvent was removed using high vacuum. The residue was subjected to flash column chromatography using methylene chloride/methanol/ triethylamine (93:5:2) to give the title compound as a white solid (67 mg, 56% yield). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 10.52 (s, 1H), 7.97 (s, 1H), 7.54 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 10.7 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.94 (t, J = 8.6 Hz, 1 H), 6.67 (d, J = 7.6 Hz, 1H), 5.64 (d, J = 7.9 Hz, 1H), 5.16 (dd, J = 15.0, 6.7 Hz, 1H), 4.56-4.49 (m, 1H), 4.25 (s, 2H), 4.11 (br t, J = 15.6 Hz, 2H), 3.92-3.84 (m, 4H), 3.73-3.69 (m, 1H),

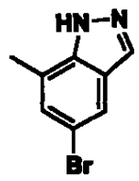
3.60-3.56 (m, 1H), 3.48-3.43 (m, 1H), 3.22-3.17 (m, 1H), 3.11 (d, J = 6.7 Hz, 2H), 2.90-2.85 (m, 2H), 2.68-2.60 (m, 4H), 1.67-1.61 (m, 2H), 1.54-1.49 (m, 2H). Mass spec.: 588 $(MH)^+$.

4-Bromo-2,6-dimethylphenyldiazo-t-butyl sulfide



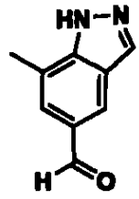
4-Bromo-2,6-dimethylaniline (20.00 g, 100 mmol) was ground to a powder with a mortar and pestle and then suspended in 24% hydrochloric acid (41 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (7.24 g, 1.05 equiv) in water (16 mL), dropwise over 40 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (11.3 mL, 1 equiv) in ethanol (100 mL) at 0°C over ca. 10 min. Following addition, the mixture was stirred at 0°C for 30 min and then crushed ice (ca. 150 mL) was added. The mixture was stored in the refrigerator overnight. The resulting light-brown solid was collected by filtration, washed with water, and dried under high vacuum for several h. (26.90 g, 89%). The compound appeared to be stable as a solid but underwent significant decomposition when recrystallization from ethanol was attempted. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.58 (9H, s), 1.99 (6H, s), 7.21 (2H, s). Mass spec.: 303.05 $(MH)^+$.

5-Bromo-7-methylindazole



Into a flame-dried round bottom flask, 4-bromo-2,6-dimethylphenyldiazo-t-butyl sulfide (12.50 g, 41.5 mmol) and potassium t-butoxide (46.56 g, 10 equiv) were combined. A stir bar was added and the mixture placed under nitrogen. To this was added dry DMSO (120 mL). The mixture was stirred vigorously overnight at rt. The reaction mixture was then carefully poured into a mixture of crushed ice (400 mL) and 10% hydrochloric acid (200 mL). The resulting suspension was left to stand at 4°C overnight and the solid was collected by filtration and washed with water. The crude solid was dissolved in 5:1 methylene chloride/methanol and the solution dried over magnesium sulfate and evaporated to give the product as an off-white solid (7.60 g, 87%). ^{1}H-NMR ($CDCl_3/CD_3OD$, 500 MHz) δ 2.51 (3H, s), 7.22 (1H, s), 7.69 (1H, s), 7.94 (1H, s). Mass spec.: 211.03 $(MH)^+$.

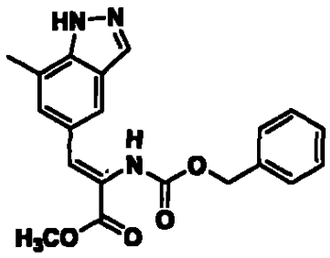
7-methylindazole-5-carboxaldehyde



5-Bromo-7-methylindazole (6.10 g, 28.9 mmol) and sodium hydride (60% in mineral oil, 1.27 g, 1.1 equiv) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (30 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -70°C and a solution of *sec*-butyllithium in cyclohexane (1.4M, 45 mL, 2.2 equiv) was added over several minutes. After 1 h at -70°C, dimethylformamide (10 mL) was added over several minutes. The mixture was allowed to warm to room temperature and was stirred overnight. It was then cooled to 0°C and carefully treated with 1N hydrochloric acid (60 mL). After a few minutes, solid sodium bicarbonate was added to basify the mixture to pH 9-10. The layers were separated and the aqueous phase washed twice with ethyl acetate. The combined organic phases were extracted with 0.8M sodium hydrogen sulfate (3 x 125 mL). The combined aqueous phases were washed with ethyl acetate (100 mL) and then the pH was adjusted to ca. 10 with solid sodium hydroxide. The resulting

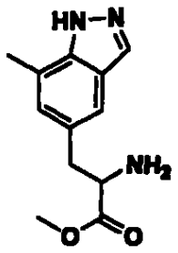
suspension was extracted with ethyl acetate (3 x 150 mL). The combined organic phases were washed with brine, dried (magnesium sulfate) and evaporated to give the product as a light-tan solid (3.01 g, 65%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.63 (3H, s), 7.73 (1H, s), 8.12 (1H, s), 8.25 (1H, s), 10.03 (1H, s). Mass spec.: 161.06 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(7-methyl-1H-indazol-5-yl)-acrylic acid methyl ester



A stirred solution of N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (5.51 g, 1.2 equiv.) in tetrahydrofuran (30 mL) at room temperature was treated with tetramethylguanidine (1.91 mL, 1.1 equiv). After 10 min, 7-methylindazole-5-carboxaldehyde (2.22 g, 13.86 mmol) in tetrahydrofuran (20 mL) was added. Disappearance of starting material was monitored by TLC and LC/MS. After 5 days at room temperature, the solvent was evaporated and the residue dissolved in ethyl acetate. The solution was washed with 2% phosphoric acid and brine, dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography on silica gel, eluting with 1) 1:1 and 2) 2:1 ethyl acetate/hexane, to give the product as a colorless foam (4.93 g, 97%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.43 (3H, s), 3.80 (3H, s), 5.12 (2H, s), 6.66 (1H, s), 7.28 (5H, brs), 7.33 (1H, s), 7.47 (1H, s), 7.74 (1H, s), 7.96 (1H, s). Mass spec.: 366.16 $(MH)^+$.

(±)-2-Amino-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester



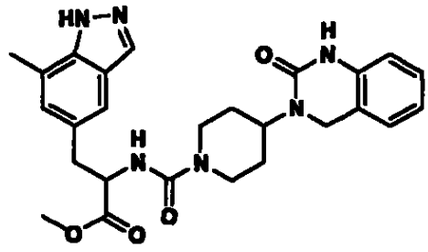
A solution of 2-benzyloxycarbonylamino-3-(7-methyl-1H-indazol-5-yl)-acrylic acid methyl ester (4.93 g, 13.49 mmol) in methanol (125 mL) was degassed

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by bubbling nitrogen through it for 30 min and then 10% palladium on charcoal (0.6 g) was carefully added. The mixture was hydrogenated at 40 psi in a Parr shaker apparatus overnight. The catalyst was removed by filtration through a pad of celite and the filtrate was concentrated *in vacuo* to give the product as a colorless foam (3.62 g, quant.). ^{1}H-NMR (CD_3OD, 500 MHz) δ 2.45 (3H, s), 2.99 (1H, Abq), 3.22 (1H, Abq), 3.74 (3H, s), 3.89 (1H, m), 6.91 (1H, s), 7.31 (1H, s), 7.73 (1H, s). Mass spec.: 234.11 $(MH)^+$.

Example 12

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester

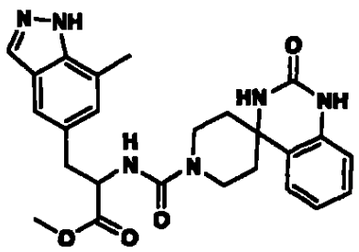


A stirred solution of (±)-2-amino-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester (162.9 mg, 0.698 mmol) in methylene chloride (3 mL) at room temperature was treated with carbonyl diimidazole (113.2 mg, 1 equiv). After 1.5 h at room temperature, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (161.5 mg, 1 equiv.) was added. The mixture was stirred at room temperature overnight. A white precipitate had formed that was shown to be the desired product. The solvent was evaporated and the residue triturated with methylene chloride. The product was collected by filtration, washed with methylene chloride and dried in vacuo to give a white solid (241.5 mg, 71%). Some product remained in the mother liquors. ^{1}H-NMR (dimethylformamide-d_7, 500 MHz) δ 1.75 (4H, m), 2.78 (3H, s), 2.7-3.1 (4H, m), 3.35 (2H, m), 3.86 (3H, s), 4.44 (2H, s), 4.57 (1H, m), 4.72 (1H, m), 7.11 (3H, m), 7.31 (1H, s), 7.34 (2H, m), 7.72 (1H, s), 9.34 (1H, s). Mass spec.: 491.13 $(MH)^+$.

Similarly prepared:

Example 13

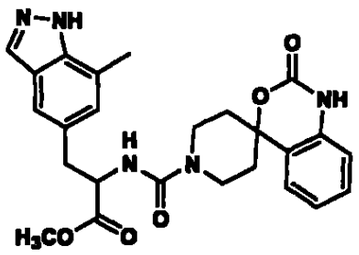
3-(7-Methyl-1H-indazol-5-yl)-2-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-(1H)-quinazoline)carbonyl amino]-propionic acid methyl ester



^{1}H-NMR (DMSO-d_6) δ 1.59 (4H, m), 2.46 (3H, s), 3.00 –3.08 (4H, m), 3.6 (3H, s), 3.78-3.81 (2H, m), 4.30-4.32 (1H, m),6.78-6.88 (4H, m), 7.03 (1H, s), 7.10 (IH, m),7.13 (1H, s),7.41 (1H,s), 7.96 (1H, s), 9.12 (1H, s). Mass spec.: 477.11 $(MH)^+$.

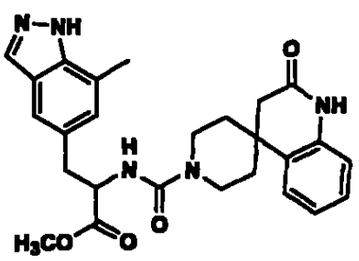
Example 14

3-(7-Methyl-1H-indazol-5-yl)-2-(1,2-dihydro-2-oxospiro-4H-3,1-dihydro-benzoxazine-4'4-piperidine-carbonylamino)-propionic acid methyl ester



Mass spec.: 478.15 $(MH)^+$.

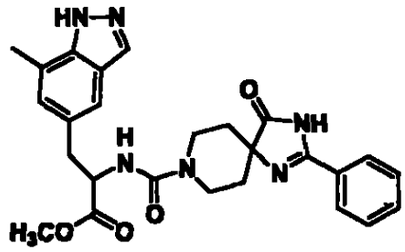
3-(7-Methyl-1H-indazol-5-yl)-2{3',4'-dihydro-2'-oxospiro-(piperidine-4,4'-(1H)-quinolinecarbonyl amino}-propionic acid methyl ester



^{1}H-NMR (DMSO-d_6) δ 1.42-1.56 (4H, m), 2.47 (3H, s), 2.50-2.54 (1H, d), 2.60-2.64 (1H, d), 2.98-3.06 4H, m), 3.60 (3H, s) 3.80 (2H, m), 4.30 (1H, m), 6.86 (2H, d), 6.95

(2H, m), 7.15 (1H, m), 7.40 (1H, s), 7.95 (1H, s), 8.32 (1H, s), 10.14 (1H, s), 13.05 (1H, s). Mass spec.: 476.17 $(MH)^+$.

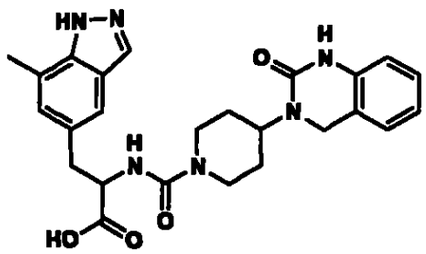
3-(7-Methyl-1H-indazol-5-yl)-2-[2'-phenyl-1',3',8'-triaza-spiro(4',5')deo-1-ene-8-carbonyl amino]-propionic acid methyl ester



^{1}H-NMR (DMSO-d_6) δ 1.50 (2H, m), 1.68 (2H, m), 2.46 (3H, s was overlapped with DMSO), 3.05 (2H, m), 3.30 (2H, m), 3.60 (3H, s), 3.86 (2H, m), 4.28 (1H, m), 6.98 (1H, d), 7.04 (1H, s), 7.40 (1H, s), 7.58 (2H, m), 7.65 (1H, m), 8.00 (1H, s), 8.04 (2H, m). Mass spec.: 489.15 $(MH)^+$.

Example 15

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid

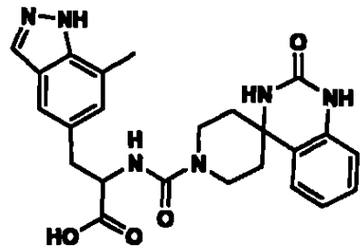


A suspension of (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (240.0 mg, 0.489 mmol) in 1:1 tetrahydrofuran/methanol (20 mL) at room temperature was treated with a solution of lithium hydroxide (140.5 mg, 7 equiv) in water (10 mL). Within 1 min, the mixture became homogeneous and it was left to stand at 4°C overnight. The solvents were evaporated at ca. 30°C and the pH was adjusted to ca. 1 with 1N hydrochloric acid. The resulting white suspension was stored at 4°C for several hours and the product was collected by filtration, washed with a small amount of water, and dried in vacuo (169.0 mg, 73%). Solid sodium

chloride was added to the filtrate resulting in precipitation of more product (5.2 mg, total yield 75%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.2-1.7 (4H, m), 2.58 (3H, s), 2.5-3.2 (4H, m), 3.35 (2H, m), 4.15 (2H, m), 4.36 (1H, m), 4.60 (1H, m), 6.79 (1H, d), 6.96 (1H, t), 7.18 (3H, m), 7.49 (1H, s), 8.00 (1H, s). Mass spec.: 477.13 $(MH)^+$.

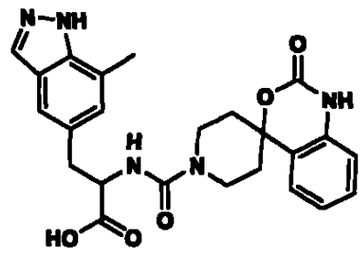
Similarly prepared:

3-(7-Methyl-1H-indazol-5-yl)-2-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-(1H)-quinazolinecarbonyl amino]-propionic acid



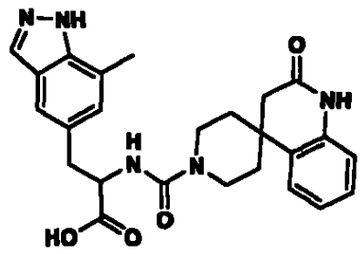
^{1}H-NMR (DMSO-d_6) δ 1.58 (4H, m), 2.46 (3H, s), 3.00-3.23 (3H, m), 3.78-3.91 (3H, m), 3.88 (2H, m) 4.28 (1H, s), 6.70 (1H, d), 6.75-6.85 (3H, m), 7.04 (1H, d), 7.11 (1H, m) 7.18 (1H, s), 7.96 (1H, s), 13.02 (1H, m). Mass spec.: 463.09 $(MH)^+$.

3-(7-Methyl-1H-indazol-5-yl)-2-(1,2-dihydro-2-oxospiro-4H-3,1-dihydro-benzoxazine-4'4-piperidine-carbonylamino)-propionic acid methyl ester



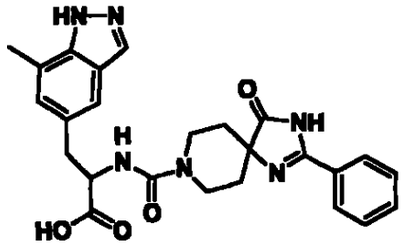
^{1}H-NMR (DMSO-d_6) δ 1.63-1.98 (4H, m), 2.46 (3H, s, 7-Me was overlapped with DMSO), 2.98-3.32 (4H, m), 3.90 (2H, m), 4.28 (1H, m), 6.78 (1H, d), 6.87 (2H, m), 6.96 (1H, m), 7.05 (1H, s), 7.24 (1H, m), 7.41 (1H, s), 7.96 (1H, s),10.22 (1H, s) 12.42 (1H, br.) 13.02 (1H, m). Mass spec.: 464.07 $(MH)^+$.

3-(7-Methyl-1H-indazol-5-yl)-2{3',4'-dihydro-2'-oxospiro-(piperidine-4,4'-(1H)-quinoline- carbonyl amino}-propionic acid



^{1}H-NMR (DMSO-d_6) δ 1.39-1.45 (2H, m), 1.53-1.56 (2H, m), 2.46 (3H, s), 2.50-2.54 (1H, d), 2.60-2.63 (1H, d), 2.88-3.00(3H, m), 3.09-3.11 (1H, m), 3.78-3.81 (2H, m), 4.27 (1H, m), 6.69-6.70 (1H, d), 6.86-6.87 (1H, d), 6.93-6.94 (1H, m)6.99-7.00 (1H, m), 7.05 (1H, m), 7.41 (1H, s), 7.95 (1H, s), 10.13 (1H, s), 12.50 (1H, m), 13.03 (1H, m). Mass spec.: 462 $(MH)^+$.

3-(7-Methyl-1H-indazol-5-yl)-2-[2'-phenyl-1',3',8'-triaza-spiro(4',5')deo-1-ene-8-carbonyl amino]-propionic acid

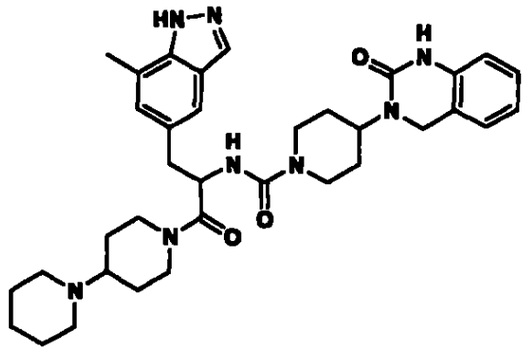


^{1}H-NMR (DMSO-d_6) δ 1.36 (2H, m), 1.63 (2H, m), 2.46 (3H, s was overlapped with DMSO), 2.98-3.03 (2H.m), 3.09-3.11 (2H, m), 3.86 (2H, m), 4.21 (1H, m), 6.69 (1H, m), 7.04 (1H, s), 7.40 (1H, s), 7.52-7.58 (3H, m), 7.99 (3H, m), 11.55 (1H, m), 13.00 (1H, m). Mass spec.: 475.08 $(MH)^+$.

Example 16

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide

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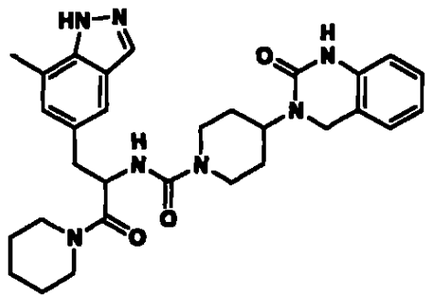


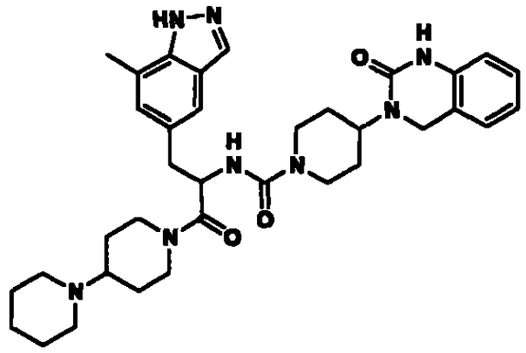
A stirred solution of (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (65.7 mg, 0.138 mmol) in 2:1 dimethylformamide/methylene chloride (1.5 mL) at 0°C was treated with 4-(1-piperidyl)-piperidne (46.5 mg, 2 equiv), diisopropylethylamine (0.048 mL, 2 equiv) and PyBOP® (75.5 mg, 1.05 equiv). The ice bath was allowed to melt and the mixture was stirred at room temperature overnight. The solvents were removed under high vacuum and the residue was purified by flash chromatography on silica gel, eluting with 18:1 methylene chloride/methanol containing 1% triethylamine, to give the product as a pale-yellow solid (80.4 mg, 93%). ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.28 (1H, m), 0.75 (1H, m), 1.2-2.0 (12H, m), 2.08 (2H, m), 2.4-2.5 (3H, m), 2.59 (3H, s), 2.68 (2H, m), 2.90 (4H, m), 3.08 (4H, m), 3.9-5.1 (4H, several m), 6.81 (1H, d), 6.96 (1H, t), 7.16 (3H, m), 7.49 (1H, s), 8.03 (1H, s). Mass spec.: 627.29 $(MH)^+$.

Similarly prepared:

Example 17

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide



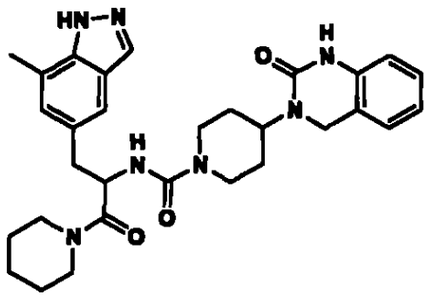


A stirred solution of (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (65.7 mg, 0.138 mmol) in 2:1 dimethylformamide/methylene chloride (1.5 mL) at 0°C was treated with 4-(1-piperidyl)-piperidne (46.5 mg, 2 equiv), diisopropylethylamine (0.048 mL, 2 equiv) and PyBOP® (75.5 mg, 1.05 equiv). The ice bath was allowed to melt and the mixture was stirred at room temperature overnight. The solvents were removed under high vacuum and the residue was purified by flash chromatography on silica gel, eluting with 18:1 methylene chloride/methanol containing 1% triethylamine, to give the product as a pale-yellow solid (80.4 mg, 93%). ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.28 (1H, m), 0.75 (1H, m), 1.2-2.0 (12H, m), 2.08 (2H, m), 2.4-2.5 (3H, m), 2.59 (3H, s), 2.68 (2H, m), 2.90 (4H, m), 3.08 (4H, m), 3.9-5.1 (4H, several m), 6.81 (1H, d), 6.96 (1H, t), 7.16 (3H, m), 7.49 (1H, s), 8.03 (1H, s). Mass spec.: 627.29 $(MH)^+$.

Similarly prepared:

Example 17

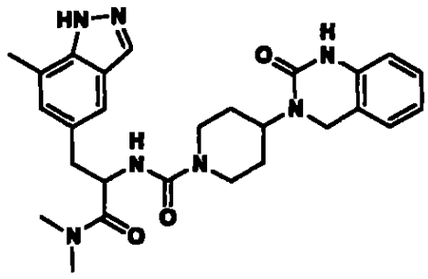
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide



^{1}H-NMR (CD_3OD, 500 MHz) δ 0.87 (1H, m), 1.33 (1H, m), 1.47 (2H, m), 1.80 (6H, m), 2.57 (3H, s), 2.89 (2H, m), 3.06 (2H, m), 3.18 (4H, m), 3.40 (2H, m), 3.61 (1H, m), 4.16 (1H, m), 4.28 (1H, Abq), 4.43 (1H, m), 5.02 (1H, m), 6.51 (1H, d), 6.79 (1H, d), 6.96 (1H, t), 7.11 (1H, d), 7.15 (1H, t), 7.48 (1H, s), 8.01 (1H, s). Mass spec.: 544.24 $(MH)^+$.

Example 18

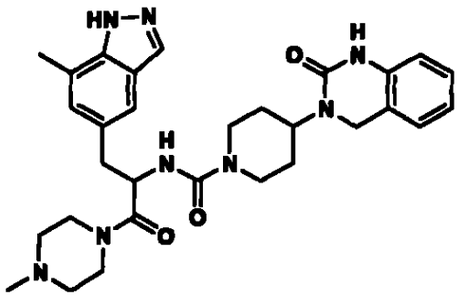
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(7-methyl-1H-indazol-5-yl)-ethyl]-amide



^{1}H-NMR (CD_3OD, 500 MHz) δ 1.12 (2H, d), 1.64 (2H, m), 2.57 (3H, s), 2.74 (1H, m), 2.87 (3H, s), 2.89 (3H, s), 2.86 (2H, m), 3.07 (2H, m), 3.20 (1H, m), 4.17 (1H, m), 4.25 (1H, Abq), 4.43 (1H, m), 4.97 (1H, m), 6.79 (1H, d), 6.95 (1H, t), 7.0-7.4 (3H, m), 7.48 (1H, d), 8.01 (1H, s). Mass spec.: 504.15 $(MH)^+$.

Example 19

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide

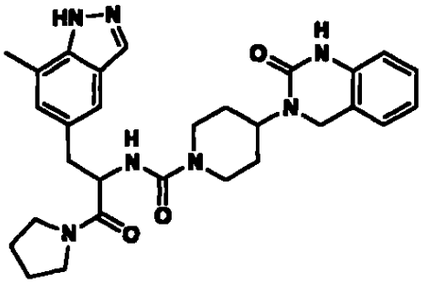


^{1}H-NMR (CD_3OD, 500 MHz) δ 1.30 (2H, m), 1.66 (2H, m), 1.78 (1H, m), 1.90 (1H, m), 2.00 (3H, s), 2.19 (1H, m), 2.35 (1H, m), 2.58 (3H, s), 2.88 (2H, m), 3.09 (2H, d), 3.10-3.45 (3H, m), 3.66 (1H, m), 4.19 (2H, d), 4.20 (2H, s), 4.43 (1H, m), 4.98 (1H,

t), 6.80 (1H, d), 6.95 (1H, t), 7.11 (2H, m), 7.16 (1H, t), 7.47 (1H, s), 8.02 (1H, s). Mass spec.: 559.23 $(MH)^+$.

Example 20

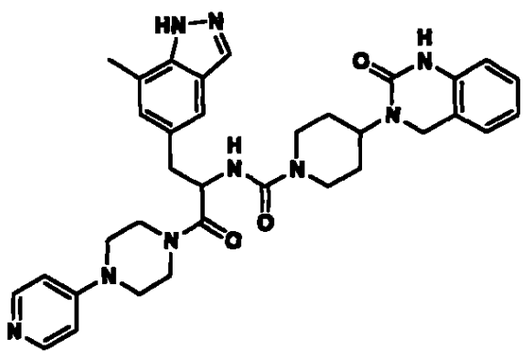
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-pyrrolidin-1-yl-ethyl]-amide



^{1}H-NMR (CD_3OD, 500 MHz) δ 1.40-1.90 (5H, m), 2.02 (3H, brs), 2.57 (3H, s), 2.86 (1H, m), 2.89 (2H, q), 3.09 (2H, m), 3.16 (1H, m), 3.25 (2H, m), 3.40 (1H, m), 3.56 (1H, m), 4.17 (2H, d), 4.27 (2H, s), 4.40 (1H, m), 4.69 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.10 (1H, s), 7.16 (1H, m), 7.48 (1H, s), 7.53 (1H, m), 8.01 (1H, s). Mass spec.: 530.19 $(MH)^+$.

Example 21

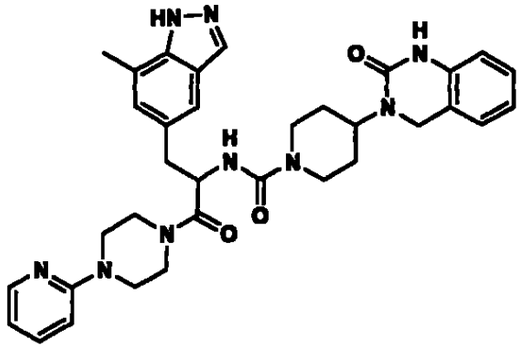
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



^{1}H-NMR (CD_3OD, 500 MHz) δ 1.38 (1H, t), 1.68 (2H, m), 1.81 (1H, m), 2.30 (1H, m), 2.53 (3H, s), 2.95 (4H, m), 3.13 (2H, d), 3.22 (1H, m), 3.35-3.65 (4H, m), 3.79 (1H, m), 4.18 (2H, d), 4.31 (2H, s), 4.42 (1H, m), 4.99 (1H, t), 6.64 (2H, d), 6.80 (1H, d), 6.89 (1H, m), 6.96 (1H, t), 7.14 (3H, m), 7.51 (1H, s), 7.99 (1H, s), 8.10 (2H, d), 8.16 (1H, m). Mass spec.: 622.26 $(MH)^+$.

Example 22

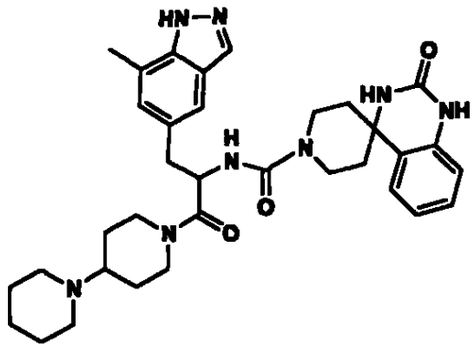
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-2-yl-piperazin-1-yl)-ethyl]-amide



^{1}H-NMR (CD_3OD, 500 MHz) δ 1.27 (1H, m), 1.38 (1H, m), 1.67 (2H, m), 1.84 (1H, m), 2.54 (3H, s), 2.65 (1H, m), 2.88 (2H, m), 3.15 (4H, m), 3.35 (1H, m), 3.58 (3H, m), 3.77 (1H, m), 4.18 (2H, d), 4.30 (2H, s), 4.42 (1H, m), 5.01 (1H, t), 6.62 (1H, d), 6.70 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.10 3H, m), 7.50 (1H, s), 7.54 (1H, t), 7.99 (1H, s), 8.05 (1H, 7). Mass spec.: 622.25 $(MH)^+$.

Example 23

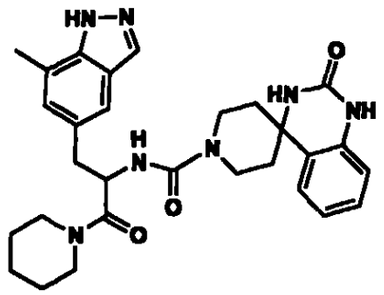
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.2-1.73 (14H, m), 2.46 (3H, s), 2.75-3.24 (12H, m), 3.87 (2H, m), 4.45 (1H, m), 4.78-4.85 (1H, m), 6.80 (1H,m), 6.86 (1H, m), 7.05 (1H, m), 7.12 (1H, m), 7.21 (1H, m), 7.27 (2H, m), 7.98 (1H, m), 9.23 (1H, m). Mass spec.: 613.25 $(MH)^+$

Example 24

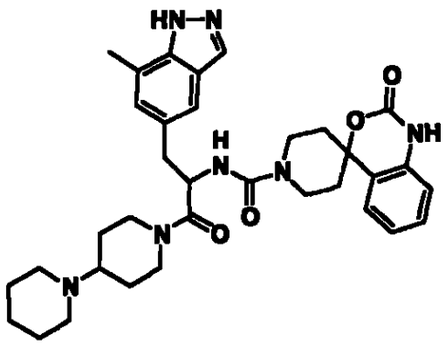
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-(1-piperidinyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



^{1}H-NMR (CD_3OD, 500 MHz) δ 0.87 (1H, m), 1.28-1.47 (5H, m), 1.74-1.85 (4H, m), 2.53 (3H, s), 3.02-3.38 (8H, m), 3.92 (2H, m), 5.02 (1H, m), 6.82 (1H, d), 6.99 (1H, d), 7.04-7.09 (2H, m), 7.17 (1H, m), 7.32 (2H, s), 7.45 (1H, s), 7.96 (1H, s). Mass spec.: 530.17 $(MH)^+$.

Example 25

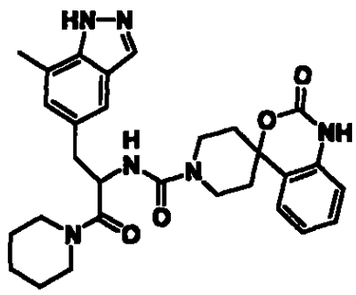
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-1',2'-dihydro-2'--oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



^{1}H-(DMSO-d_6, 500 MHz) δ 1.88 (14H, m), 2.64 (3H, s), 2.78 (12H,m), 4.0 (2H, m), 4.4 (1H, m),4.85 (1H, m), 6.80-6.88 (2H, m), 7.03 (2H, m), 7.11 (1H, m), 7.23 (1H, m), 7.36 (2H, m), 7.97 (1H, m). Mass spec.: 614.73 $(MH)^+$.

Example 26

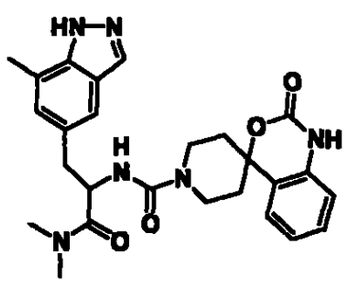
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-(1-piperidinyl)-2-oxoethyl]-1',2'-dihydro-2'--oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.15-1.91 (10H, m), 2.47 (3H, s), 2.95-3.05 (6H, m) 3.40 (4H, m) 3.95 (2H, d), 4.81(1H, m), 6.81 (1H, d), 6.88 (1H, d), 6.94 (1H, m), 6.99 (1H, m), 7.04 (1H, s), 7.24 (1H, m), 7.37 (1H, s), 7.96 (1H, s). Mass spec.: 531.23 $(MH)^+$.

Example 27

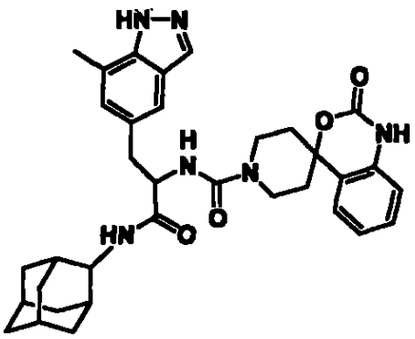
(±)-[1-Dimethylcarbamoyl-2-(7-methyl-1H-indazol-5-yl)-ethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.68-1.88 (4H, m), 2.47 (3H, m), 2.79 (6H, s), 2.89-3.04 (4H, m), 3.96 (2H, d), 4.75 (1H, m), 6.81 (1H, d), 6.88 (1H, m), 6.93 (1H, m), 6.98 (1H, m), 7.05 (1H, s), 7.24 (1H, m), 7.43 (1H, s), 7.97 (1H, m), 8.32 (1H, s). Mass spec.: 491.14 $(MH)^+$.

Example 28

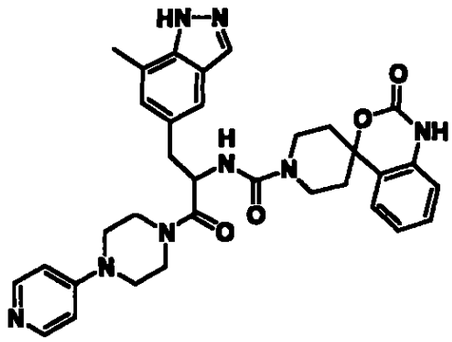
(±)-[1-(2-adamantyl-carbamoyl)-2-(7-methyl-1H-indazol-5-yl)-ethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.40-1.95 (15H, m), 2.46 (3H, m), 2.89-3.07 (4H, m), 3.81 (1H, m), 3.90 (2H, m), 4.48 (1H, m), 6.74 (2H, m), 6.86 (1H, d), 6.97 (1H, m), 7.11 (1H, s), 7.24 (1H, m), 7.36 (1H, s), 7.44 (1H, s), 7.96 (1H, s). Mass Spec.: 597.27 $(MH)^+$.

Example 29

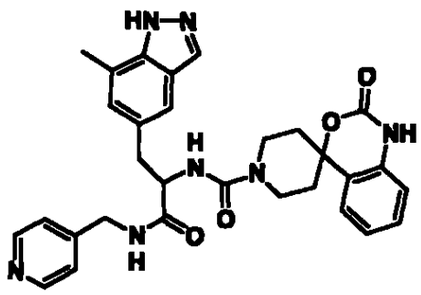
(±)-1',2'-Dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine-1-carboxylic acid [1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



LC/MS: t_R = 1.56 min, 609.14 $(MH)^+$.

Example 30

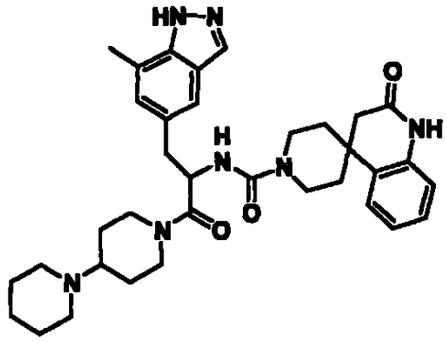
(±)-1',2'-Dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine-1-carboxylic acid {2-(7-methyl-1H-indazol-5-yl)-1-[(pyridin-4-ylmethyl)-carbamoyl]-ethyl}-amide



LC/MS: t_R = 1.49 min, 553.12 $(MH)^+$.

Example 31

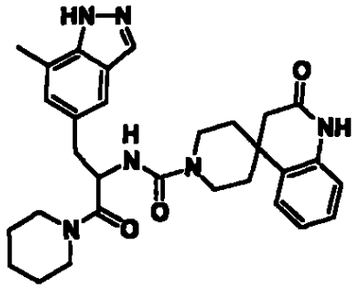
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]3',4'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinoline]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.20-2.00 (14H, m), 2.46 (3H, s), 2.38-3.03 (12H, m), 3.87 (2H, m), 4.34 (1H, m), 4.76-4.87 (1H, m), 6.65 (1H, m), 6.82-7.64 (3H, m), 7.13-7.23 (2H, m), 7.36 (3h, m), 7.96 (1H, s). Mass spec.: 612.32 $(MH)^+$.

Example 32

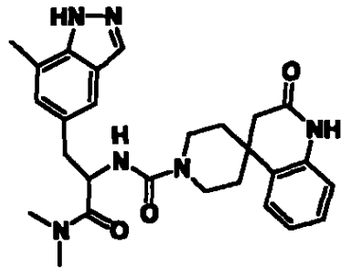
(±)- 1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-piperidinyl]-2-oxoethyl]3',4'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinoline]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.10-1.68 (10H, m), 2.46 (3H, s), 2.50-2.60 (2H, m), 2.82-2.97 (4H, m), 3.39 (2H, m), 3.85 (2H, m), 4.80 (1H, m), 6.68 (1H, m), 6.87 (1H, d), 6.94 (1H, m), 7.03 (1H, s), 7.06 (1H, m), 7.15 (1H, m), 7.37 (1H, s), 7.40 (1H, s), 7.96 (1H, s). Mass spec.: 529.25 $(MH)^+$.

Example 33

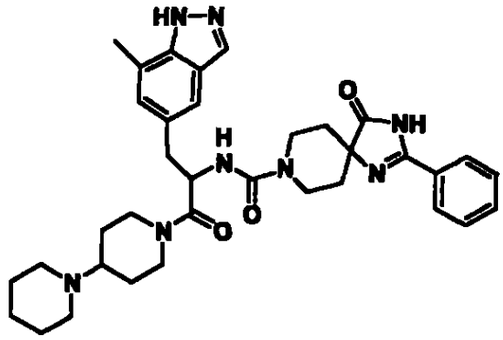
(±)-[1-Dimethylcarbmoyl-2-(7-methyl-1H-indazol-5-yl)-ethy]l-3',4'-dihydro -2'-oxospiro- [piperidine-4,4'-(1H)-quinoline]-1-carboxamide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.43 (2H, m), 1.56 (2H, m), 2.46 (3H, s), 2.56 (2H, m), 2.79 (3H, s), 2.90 (5H, m), 3.84 (2H, m), 4.73 1H, m), 6.69 (1H, d), 2.69 (1H, d), 6.94 (1H, m), 7.05 (2H, m), 7.14 (1H, m), 7.37 (1H, s), 7.42 (1H, s), 7.96 (1H, s). Mass spec.: 489.2 $(MH)^+$.

Example 34

(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid{1-(7-methyl-1H-indazol-5- yl methyl)-2-[1,4]bipiperidinyl-1'-yl-2-oxo-ethyl}-amide



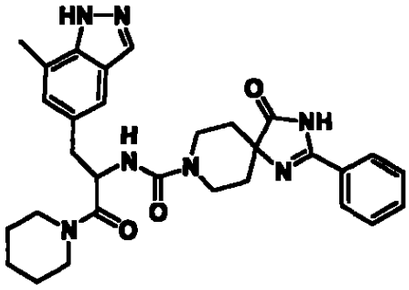
^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.34-2.00 (14H, m), 2.48 (3H, s overlapped with DMSO), 2.70-3.30 (12H, m), 3.90 (2H, m), 4.40 (1H, m), 4.82 (1H, m), 6.82 (1H,

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m), 7.04 (1H, s), 7.37 (2H, m), 7.56 (3H, m), 7.98 (3H, m). Mass spec.: 625.29 $(MH)^+$.

Example 35

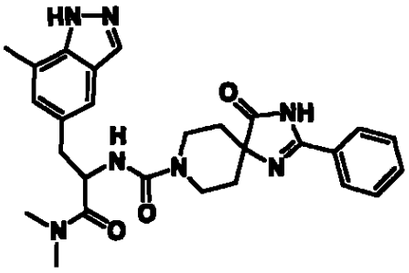
(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid{1-(7-methyl-1H-indazol-5- yl methyl)-2-[1-piperidinylyl]-2-oxo-ethyl}-amide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.10-1.62 (6H, m), 1.73 (4H, m), 2.48 (3H, s), 3.00 (6H, m), 3.39 (2H, m), 3.93 (2H, m), 4.82 (1H, m), 6.78 (1H, m), 7.05 (1H, s), 7.37 (2H, s), 7.40 (1H, s), 7.53 (2H, m), 7.98 (2H, m). Mass spec.: 543.26 $(MH)^+$.

Example 36

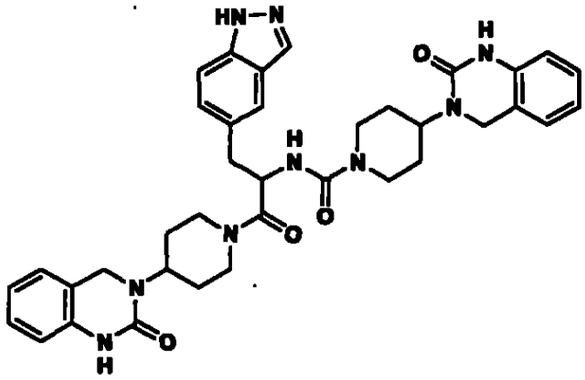
(±)-4-Oxo-2-phenyl-1,3,8-triaza-spiro[4,5]dec-1-ene-8-carboxylic acid[1-dimethylcarbamoyl -2-(7-methyl-1H-indazol-5- yl)-ethyl]amide



^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.28-1.61 (4H, m), 2.78 (4H, m), 2.90 (6H, m), 3.94 (2H, m), 4.74 (1H, m), 6.77 (1H, m), 7.05 (1H, s), 7.37 (4H, s), 7.42 (1H, s), 7.52 (2H, m), 7.98 (2H, m). Mass spec.: 502.21 $(MH)^+$.

Example 37

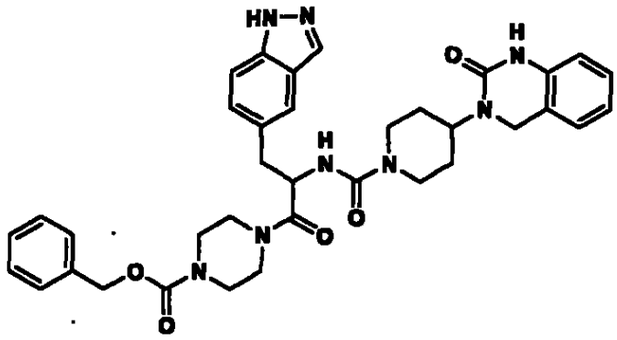
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {1-(1H-indazol-5-ylmethyl)-2-oxo-2-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-ethyl}-amide



LC/MS: t_R = 1.51 min, 674 $(MH)^-$.

Example 38

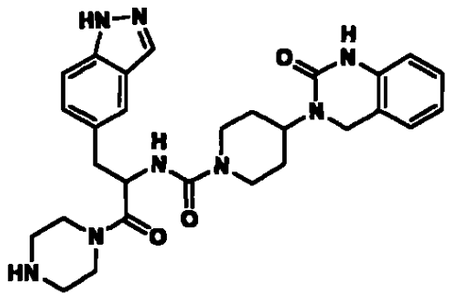
4-(3-(1H-Indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyl)-piperazine-1-carboxylic acid benzyl ester



LC/MS: t_R = 1.74 min, 665 $(MH)^+$.

Example 39

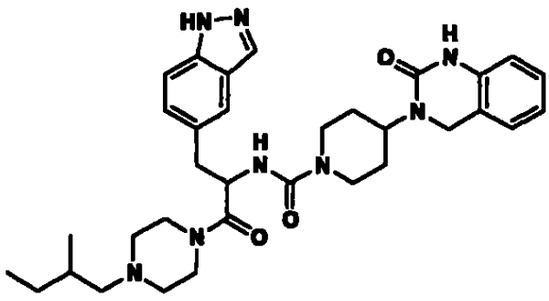
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-oxo-2-piperazin-1-yl-ethyl]-amide



To a degassed solution of 4-(3-(1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyl)-piperazine-1-carboxylic acid benzyl ester (280 mg, 0.42 mmol) in methanol (50 ml) was added 10% palladized charcoal (50 mg). The mixture was shaken in a Parr apparatus under an atmosphere of hydrogen at 50 psi for 3 h. The mixture was filtered through celite. The filtrate was concentrated under reduced pressure to give the desired product in 91% yield. LC/MS: t_R = 1.22 min, 531 $(MH)^+$.

Example 40a

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid {1-(1H-indazol-5-ylmethyl)-2-[4-(2-methyl-butyl)-piperazin-1-yl]-2-oxo-ethyl}-amide



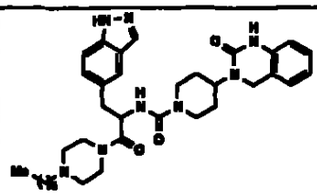
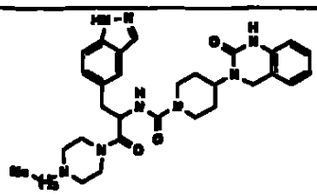
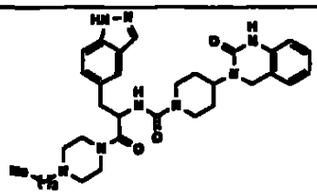
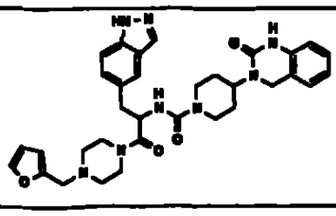
A stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(1H-indazol-5-ylmethyl)-2-oxo-2-piperazin-1-yl-ethyl]-amide (100 mg, 0.188 mmol) in methanol (25 mL) was treated with 2-methyl-butyraldehyde (0.03 ml, 0.376 mmol). After 1h at room temperature, sodium triacetoxyborohydride (80 mg, 0.316 mmol) was added. The mixture was allowed to stir overnight. The solution was filtered through an SCX cartridge. The cartridge was eluted first with methanol and then with a 1M solution of ammonia in methanol. The solvent was removed *in vacuo* to give the desired product in 50% yield. LC/MS: t_R = 1.31 min, 601$(MH)^+$.

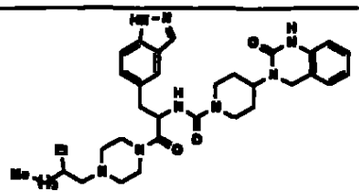
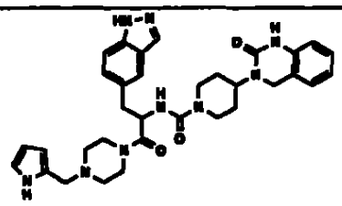
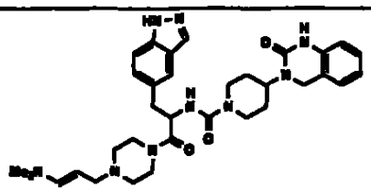
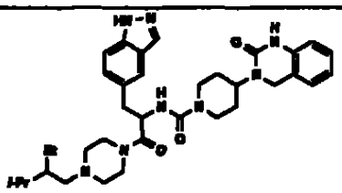
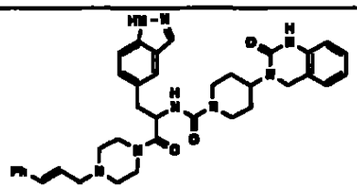
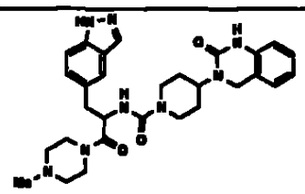
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General Experimental Procedure for the Preparation of Examples 40b-40k.

The appropriate aldehyde (0.04 mmol) was added to a solution of Example 39 piperazine (0.02 mmol) in methanol (2.0 mL) and the resulting solution was shaken at room temperature for 1 h. Sodium triacetoxyborohydride (0.2 mmol) was then added and the solution allowed stir overnight at room temperature. The solution was then filtered through a SCX cartridge and the cartridge washed with methanol and an ammonia/methanol solution. The ammonia/methanol solution was concentrated *in vacuo* and the crude products were purified by preparative HPLC to the afford the products listed in Table 1.

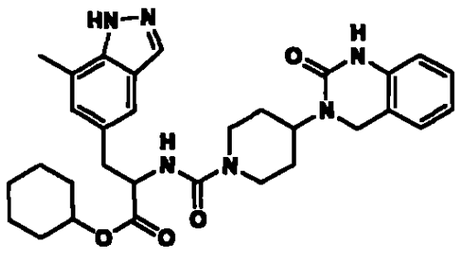
Table 1. Examples 40b-40k.

Example No.	Structure	HPLC Retention time (min)	Mass spec $(MH)^+$
40b		2.62	629
40c		1.41	587
40d		1.27	573
40e		1.74	611

Example No.	Structure	HPLC Retention time (min)	Mass spec $(MH)^+$
40f		1.89	643
40g		1.48	610
40h		2.19	614
40i		2.36	629
40j		1.66	647
40k		2.61	545

Example 41a

3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester

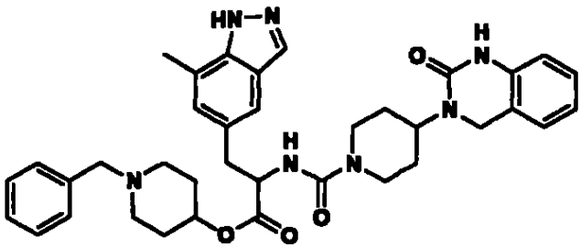


To a stirred solution of (±) –2-amino-3-(7-methyl- 1H-indazol-5-yl)-propinic acid (20 mg, 0.042 mmoles), 4-(dimethylamino)pyridine (2.5 mg, 0.02 mmoles), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (33 mg, 0.17 mmoles) in methylene chloride (2 mL) and dimethylforamide (1 mL), was added cyclohexanol (13.3 µL, 0.126 mmoles). The reaction mixture was stirred at 50-55°C for 4 h. The solvent was removed under reduced pressure, the the residue purified by preparative TLC on silica gel (9:1 chloroform/methanol) to give the desired product as white solid (9.4 mg, 40%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.32-1.87 (14H, m), 2.57 (3H, s), 2.86 (2H, m), 3.11-3.26 (2H, m), 4.13-4.22 (3H, m), 4.46 (1H, m), 4.55 (1H, m), 4.80 (1H, m), 6.79 (1H, d), 6.97 (1H, m), 7.08-7.18 (2H, m), 7.35 (1H, s), 7.47 (1H, s), 8.01-8.02 (1H, m). Mass spec.: 559.22 $(MH)^+$.

Similarly prepared:

Example 41b

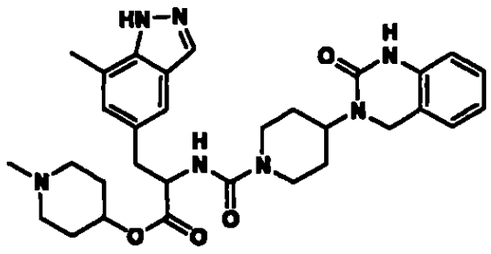
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-benzyl-piperidin-4-yl ester



LC/MS: t_R = 1.76 min, 650.30 $(MH)^+$.

Example 41c

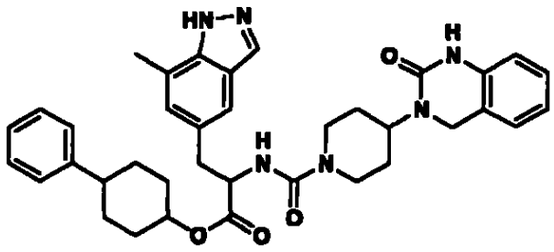
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester



LC/MS: t_R = 1.59 min, 574.27 $(MH)^+$.

Example 41d

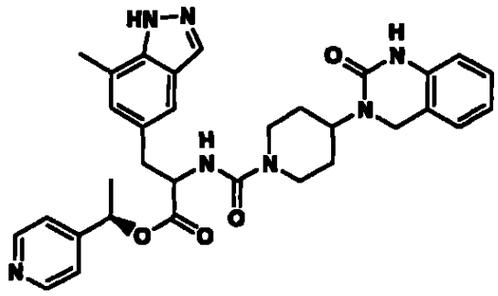
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester



LC/MS: t_R = 2.69 min, 635.29 $(MH)^+$.

Example 41e

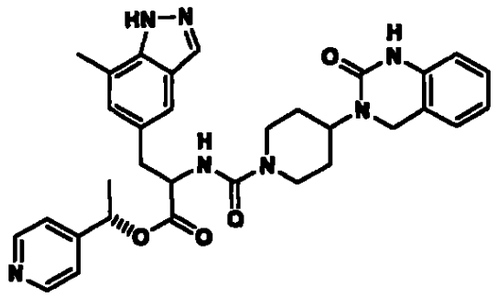
3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (R)-1-pyridin-4-yl-ethyl ester



LC/MS: t_R = 1.66 min, 582.22 $(MH)^+$.

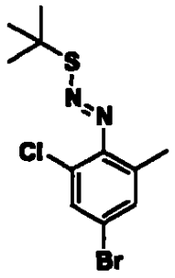
Example 41f

3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid (S)-1-pyridin-4-yl-ethyl ester



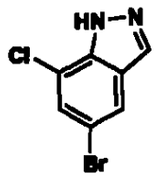
LC/MS: t_R = 1.65 min, 582.23 $(MH)^+$.

4-Bromo-2-chloro-6-methylphenyldiazo-t-butyl sulfide



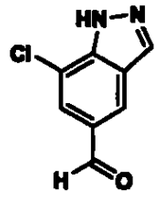
4-Bromo-2-chloro-6-methylaniline (4.0 g, 18.3 mmol) was suspended in 24% hydrochloric acid (5 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (1.32 g, 1.05 equiv.) in water (2 mL), dropwise over 10 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (2.06 mL, 1 equiv.) in ethanol (18.5 mL) at 0°C over ca. 10 min. Following addition, the mixture was stirred at 0°C for 30 min and then crushed ice (ca. 50 mL) was added. The mixture was stored in the refrigerator overnight. The resulting light-brown solid was collected by filtration, washed with water, and dried under high vacuum for several hours (4.60 g, 78%). Mass spec.: 323.03 $(MH)^+$.

5-Bromo-7-chloroindazole



Into a flame-dried round bottom flask, 4-bromo-2,-chloro-6-methylphenyldiazo-t-butyl sulfide (4.60 g, 14.4 mmol) and potassium t-butoxide (16.1 g, 10 equiv) were combined. A stir bar was added and the mixture placed under nitrogen. To this was added dry DMSO (50 mL). The mixture was stirred vigorously for 10 min at room temperature. The reaction mixture was then carefully poured into a mixture of crushed ice (150 mL) and 10% hydrochloric acid (74 mL). The resulting suspension was left to stand at 4°C overnight and the solid was collected by filtration and washed with water. The solid was collected and dried in vacuo to give 2.86 g (86%) as a beige solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, J=1.5, 1H), 7.82 (d, J=1.5, 1H), 8.08 (s, 1H). Mass spec.: 230.90 $(MH)^+$.

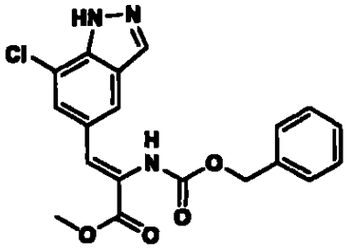
7-Chloroindazole-5-carboxaldehyde



5-Bromo-7-chloroindazole (2.0 g, 8.7 mmol) and sodium hydride (221 mg, 1.1 equiv) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (30 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -78°C and a solution of *tert*-butyllithium in pentane (1.7 M, 10.5 mL, 2.0 equiv) was added over several minutes. After 30 min at -78°C, the reaction was gradually warmed to to –50°C, kept there for 15 min, and recooled to –78°C. Dimethylformamide (2.8 mL) was slowly added and the mixture allowed to warm to –50°C. The solution was quickly transferred to a separatory funnel containing diethyl ether and water. The aqueous was made acidic by the addition of 1 M potassium hydrogen sulfate and neutralized by the addition of sodium bicarbonate. The aqueous was extracted with diethyl ether (3x) which was washed with water, then brine, dried over magnesium sulfate, and concentrated to give 1.7g (100%) of nearly pure material. An analytically pure sample was obtained by recrystallization from hot methanol. ^{1}H-

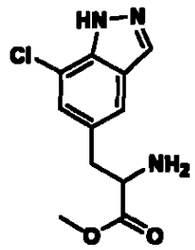
NMR ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 8.20 (s, 1H), 8.30 (s, 1H), 10.02 (s, 1H). Mass spec.: 181.09 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(7-chloro-1H-indazol-5-yl)-acrylic acid methyl ester



A stirred suspension of potassium *tert*-butoxide (375 mg, 1.2 equiv.) in methylene chloride (20 mL) was cooled to –20°C and treated with a solution of N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (1.11 g, 1.2 equiv.) in methylene chloride (5 mL). After 10 min, 7-chloroindazole-5-carboxaldehyde (0.50 g, 2.79 mmol) in methylene chloride (5 mL) was added. The reaction was allowed to gradually warm to room temperature and was stirred for 3 days. The reaction was poured into a separatory funnel containing water and diethyl ether. The aqueous was extracted with diethyl ether (3x) which was washed with brine, dried over magnesium sulfate, and concentrated. Column chromatography gave 0.40 g (37%) of product along with 0.20 g (40%) of starting material. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.64 (s, 3H), 5.11 (s, 2H), 6.44 (bs, 1H), 7.30 (bs, 5H), 7.43 (s, 1H), 7.62 (s, 1H), 7.80 (s, 1H), 8.07 (s, 1H). Mass spec.: 386.16 $(MH)^+$.

(±)-2-Amino-3-(7-chloro-1H-indazol-5-yl)-propionic acid methyl ester

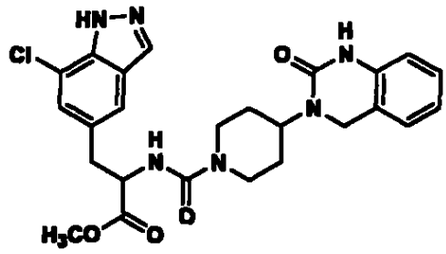


A solution of 2-benzyloxycarbonylamino-3-(7-chloro-1H-indazol-5-yl)-acrylic acid methyl ester (300 mg, 0.78 mmol) in methanol (10 mL) was treated with trifluoroacetic acid (0.2 mL), flushed with nitrogen, and treated with 10% palladium on charcoal (30 mg). The flask was flushed with hydrogen and allowed to stir under

an atmosphere of hydrogen. After 4 days, all starting material had been consumed. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 78 mg (40%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.31 (bs, 3H), 2.95 (dd, *J*=13.7, 7.9, 1H), 3.18 (dd, *J*=13.7, 5.2, 1H), 3.48 (s, 3H), 3.78 (dd, *J*=7.9, 5.2, 1H), 7.23 (s, 1H), 7.46 (s, 1H), 8.00 (s, 1H). Mass spec.: 254.06 $(MH)^+$.

Example 42

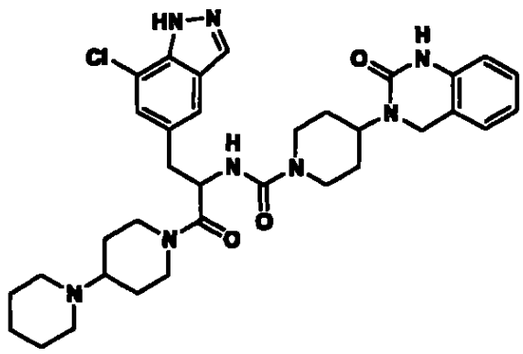
(±)-3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A stirred solution of (±)-2-amino-3-(7-chloro-1H-indazol-5-yl)-propionic acid methyl ester (78 mg, 0.31 mmol) in tetrahydrofuran (2 mL) at 0°C was treated with carbonyl diimidazole (50 mg, 1 equiv). The reaction was stirred for 5min, warmed to room temperature, stirred 10 min, and treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (78 mg, 1.1 equiv). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by column chromatography to give 148 mg (94%) as a white powder. ^{1}H-NMR (DMSO-d_6, 500 MHz) δ 1.46 (m, 4H), 2.55-2.80 (m, 2H), 3.05 (dd, *J*=13.7, 10.7, 1H), 3.15 (m, 1H), 3.62 (s, 3H), 4.04 (d, *J*=13.4, 2H), 4.11 (s, 2H), 4.22-4.39 (m, 2H), 6.76 (d, *J*=7.9, 1H), 6.87 (dd, *J*=7.3, 7.3, 1H), 6.90 (d, *J*=8.2, 1H), 7.08 (d, *J*=7.6, 1H), 7.12 (dd, *J*=7.6, 7.6, 1H), 7.40 (s, 1H), 7.60 (s, 1H), 8.15 (s, 1H), 9.18 (s, 1H), 13.48 (s, 1H). Mass spec.: 511.18 $(MH)^+$.

Example 43

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



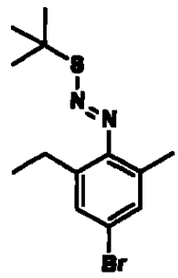
A suspension of (±)-3-(7-chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (15 mg, 0.029 mmol) in 1:1 tetrahydrofuran /methanol (1 mL) at room temperature was treated with a solution of lithium hydroxide (3.0 mg, 2.5 equiv) in water (0.25 mL), and the resulting solution was stirred for 1.5 h. The solution was cooled to 0°C, treated with aqueous 1 M potassium hydrogen sulfate (60 µL, 2.0 equiv), and concentrated to give the crude acid which was immediately used without purification. The crude acid was dissolved in dimethylformamide (0.3 mL) and sequentially treated with methylene chloride (0.15 mL), 4-piperidyl-piperidine (10.1 mg, 2 equiv), diisopropylethylamine (10 µL, 2 equiv), and PyBOP® (16.5 mg, 1.1 equiv). The solution was stirred 30 min and concentrated. The product was purified by column chromatography to give 14.7 mg (77%, 2 steps). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 8H), 1.65-1.88 (m, 5H), 2.14 (m, 1H), 2.23 (m, 1H), 2.30-2.70 (m, 7H), 2.80-3.20 (m, 5H), 3.94 (d, *J*=13.4, 13.1, 1H), 4.10-4.30 (m, 4H), 4.55 (m, 1H), 4.62 (dd, *J*=13.1, 12.8, 1H), 5.19 (m, 1H), 5.91 (dd, *J*=30.2, 22.3, 1H), 6.70 (d, *J*=7.6, 1H), 6.92 (dd, *J*=7.6, 7.3, 1H), 7.01 (dd, J, 7.9, 7.6, 1H), 7.13 (s, 0.4H), 7.15 (dd, *J*=7.9, 7.6, 1H), 7.24 (s, 0.6H), 7.33 (s, 0.4H), 7.43 (s, 0.6H), 7.49 (bs, 1H), 7.91 (s, 0.4H), 7.95 (s, 0.6H), 11.25 (bd, *J*=50.7, 1H). Mass spec.: 647.37 $(MH)^+$.

4-Bromo-2-ethyl-6-methyl-phenylamine



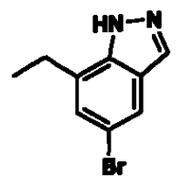
2-Ethyl-6-methyl-phenylamine (14 mL, 100 mmol) was dissolved in concentrated hydrochloric acid (30 mL) and water (220 mL) and cooled to 0°C. To this was added bromine (5.1 mL, 1 equiv.) dropwise. There was rapid formation of a white precipitate. The precipitate was filtered and washed with diethyl ether. The precipitate was suspended in water and neutralized with aqueous potassium carbonate. An oil formed which was extracted into diethyl ether. The ethereal was dried over potassium carbonate, filtered, and concentrated to give 7.0 g (33%) as a purple oil which was used without purification. Mass spec.: 214.01 $(MH)^+$.

4-Bromo-2-ethyl-6-methylphenyldiazo-t-butyl sulfide



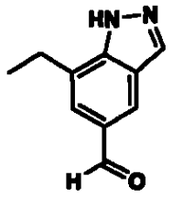
4-Bromo-2-ethyl-6-methylaniline (7.0 g, 33 mmol) was suspended in 7.8 M hydrochloric acid (30 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (2.27 g, 1.05 equiv.) in water (5 mL), dropwise over 10 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (3.7 mL, 1 equiv.) in ethanol (50 mL) at 0°C over ca. 10 min. Following addition, the mixture was stirred at 0°C for 30 min and then crushed ice (ca. 50 mL) was added. The mixture was stored in the refrigerator for 2 h. The resulting light-brown solid was collected by filtration, washed with water, and dried under high vacuum for several hours (9.47 g, 92%). Mass spec.: 315.05 $(MH)^+$.

5-Bromo-7-ethyl-1H-indazole



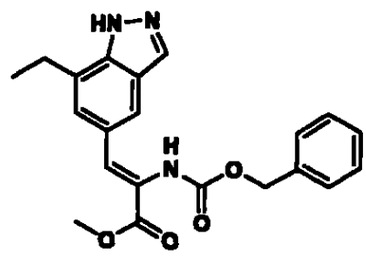
To a stirred solution of potassium t-butoxide (33.6 g, 10 equiv.) in DMSO (200 mL) was added a solution of 4-bromo-2-ethyl-6-methylphenyldiazo-t-butyl sulfide (9.4 g, 30 mmol) in DMSO (100 mL) via cannula. The mixture was stirred vigorously for 1 h. The reaction mixture was then carefully poured into a mixture of crushed ice (500 mL), concentrated hydrochloric acid (25 mL), and water (100 mL). The resulting precipitate was filtered, washed with water, dissolved in methanol, and concentrated to give 5.7 g (85%) as a tan solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.39 (t, *J*=7.6, 3H), 2.92 (q, *J*=7.6, 2H), 7.30 (s, 1H), 7.75 (s, 1H), 8.04 (s, 1H). Mass spec.: 225.00 $(MH)^+$.

7-Ethyl-1H-indazole-5-carbaldehyde



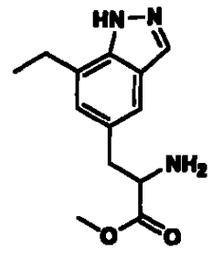
5-Bromo-7-ethyl-1H-indazole (2.0 g, 8.9 mmol) and sodium hydride (226 mg, 1.1 equiv.) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (60 mL) was added. The mixture was stirred at room temperature for 15 min. The stirred mixture was cooled to -78°C and a solution of *tert*-butyllithium in pentane (1.7 M, 10.5 mL, 2.0 equiv.) was added over several minutes. After 15 min at -78°C, the reaction was gradually warmed to to –50°C, and recooled to –78°C. Dimethylformamide (2.8 mL) was slowly added and the mixture allowed to warm to –50°C. The solution was quickly transferred to a stirred solution of water 300 mL and 1 M potassium hydrogen sulfate (25 mL). The resulting suspension was extracted with diethyl ether, washed with water, then brine, dried over magnesium sulfate, and concentrated. Column chromatography gave 160 mg (10%) as a white solid. ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.38 (t, *J*=7.6, 3H), 2.98 (q, *J*=7.6, 2H), 7.71 (s, 1H), 8.22 (s, 1H), 8.24 (s, 1H), 9.96 (s, 1H). Mass spec.: 175.08 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(7-ethyl-1H-indazol-5-yl)-acrylic acid methyl ester



To a stirred solution of N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (0.61 g, 2.0 equiv.) and 7-ethyl-1H-indazole-5-carbaldehyde (160 mg, 0.92 mmol) in tetrahydrofuran (5 mL) at 0°C was added tetramethylguanidine (0.22 mL, 1.9 equiv.). The reaction was allowed to slowly warm to room temperature overnight. The reaction was concentrated, dissolved in diethyl ether, washed with water, then brine, dried (magnesium sulfate), and concentrated. The residue was purified by column chromatography to give 333 mg (95%) as an oil. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.33 (t, *J*=7.6, 3H), 2.86 (q, *J*=7.3, 2H), 3.83 (s, 3H), 5.11 (s, 2H), 6.39 (bs, 1H), 7.29 (bs, 5H), 7.43 (s, 1H), 7.50 (s, 1H), 7.78 (s, 1H), 8.04 (s, 1H). Mass spec.: 380.17 $(MH)^+$.

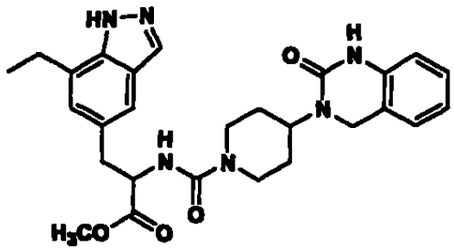
(±)-2-Amino-3-(7-ethyl-1H-indazol-5-yl)-propionic acid methyl ester



To a solution of 2-benzyloxycarbonylamino-3-(7-ethyl-1H-indazol-5-yl)-acrylic acid methyl ester (330 mg, 0.78 mmol) in methanol (5 mL) under nitrogen was added palladium on charcoal (10%, 33 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated to give 210 mg (98%) which was used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.34 (t, *J*=7.6, 3H), 2.85 (q, *J*=7.6, 2H), 2.96 (dd, *J*=13.7, 7.6, 1H), 3.19 (dd, *J*=13.7, 8.6, 1H), 3.48 (s, 2H), 3.73 (s, 3H), 3.80 (dd, *J*=7.6, 5.2, 1H), 6.99 (s, 1H), 7.38 (s, 1H), 7.97 (s, 1H). Mass spec.: 248.15 $(MH)^+$.

Example 44

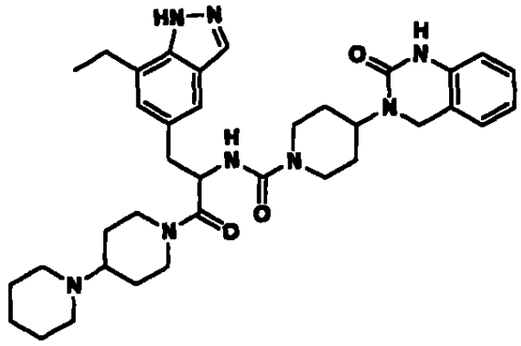
(±)-3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A stirred solution of (±)-2-amino-3-(7-ethyl-1H-indazol-5-yl)-propionic acid methyl ester (100 mg, 0.41 mmol) in tetrahydrofuran (2 mL) at 0°C was treated with carbonyl diimidazole (66 mg, 1 equiv). The reaction was stirred for 5 min, warmed to room temperature, stirred for 15 min, and then treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (103 mg, 1.1 equiv). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by column chromatography to give 188 mg (92%) as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.36 (t, *J*=7.6, 3H), 1.69 (m, 4H), 2.86 (m, 2H), 2.90 (q, *J*=7.6, 2H), 3.22 (dd, *J*=5.5, 4.9, 2H), 3.75 (s, 3H), 4.03 (dd, *J*=44.0, 13.7, 2H), 4.26 (s, 2H), 4.51 (m, 1H), 4.84 (m, 1H), 5.02 (m, 1H), 6.70 (d, *J*=7.9, 1H), 6.90-7.05 (m, 4H), 7.16 (dd, *J*=7.6, 7.6, 1H), 7.34 (s, 1H), 8.03 (s, 1H). Mass spec.: 505.29 $(MH)^+$.

Example 45

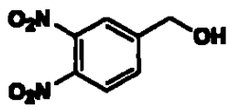
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



To a solution of (±)-3-(7-ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (15

mg, 0.03 mmol) in methanol (0.6 mL) was added a solution of lithium hydroxide monohydrate (3.0 mg, 2.5 equiv) in water (0.1 mL), and the resulting solution was stirred for 6 h. The solution was cooled to 0°C, treated with aqueous 1 M potassium hydrogen sulfate (60 μL, 2.0 equiv), and concentrated to give the crude acid which was immediately used without purification. The crude acid was dissolved in dimethylformamide (0.4 mL), cooled to 0°C, and sequentially treated with methylene chloride (0.2 mL), 4-piperidyl-piperidine (11 mg, 2.2 equiv), diisopropylethylamine (12 μL, 2.3 equiv.), and PyBOP® (19 mg, 1.2 equiv). The solution was stirred for 15 min at 0°C, warmed to room temperature, stirred 1.5 h, and concentrated. The product was purified by column chromatography to give 14.5 mg (76%, 2 steps). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.28-1.48 (m, 10H), 1.52 (m, 2H), 1.60-1.82 (m, 6H), 1.95 (m, 1.4H), 2.06 (m, 1.6H), 2.20-2.50 (m, 5H), 2.77-2.93 (m, 5H), 2.96-3.17 (m, 2H), 3.76 (d, *J*=13.4, 0.4H), 3.86 (d, *J*=13.7, 0.6H), 4.10-4.20 (m, 2H), 4.26 (s, 2H), 4.57 (m, 2H), 5.10-5.24 (m, 1H), 5.67 (d, *J*=8.2, 0.6H), 5.74 (d, *J*=7.9, 0.4H), 6.67 (d, *J*=7.9, 1H), 5.67 (d, *J*=8.2, 0.6H), 5.74 (d, *J*=7.9, 0.4H), 6.67 (d, *J*=7.9, 1H), 6.93 (dd, *J*=7.6, 7.3, 1H), 6.96 (s, 0.4H), 7.03 (dd, *J*=7.0, 6.7, 1H), 7.09 (m, 1.6H), 7.15 (dd, *J*=7.0, 6.7, 1H), 7.31 (s, 0.4H), 7.38 (s, 0.6H), 7.94 (s, 0.4H), 7.95 (s, 0.6H). Mass spec.: 641.50 $(MH)^+$.

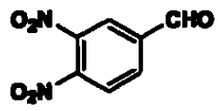
(3,4-Dinitro-phenyl)-methanol



Borane-tetrahydrofuran complex (1M in tetrahydrofuran, 800 mL, 800 mmol) was added at –20°C over 45 min to a solution of 3,4-dinitrobenzoic acid (93.5 g, 441 mmol) in tetrahydrofuran (300 mL). The resulting mixture was stirred at –20°C for 1 h and then warmed to room temperature and stirred overnight. It was quenched by the addition of 32 mL of 1:1 acetic acid/water. Solvents were removed *in vacuo* and the residue was poured into an ice-cold 1000 mL of sat. sodium bicarbonate with vigorous stirring over 15 min. The mixture was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with sat. sodium bicarbonate, brine and dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a light yellow solid (100%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ

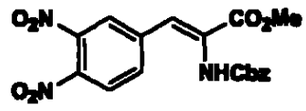
7.91(d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.71 (dd, J = 8.5, 1.0 Hz, 1H), 4.87 (s, 2H), 2.30 (s, 1H).

3,4-Dinitro-benzaldehyde



A solution of (3,4-dinitro-phenyl)-methanol (95.3g, 481 mmol) in methylene chloride (500 mL) was added all at once to a suspension of pyridinium chlorochromate (156 g, 722 mmol) in methylene chloride (900 mL). The mixture was stirred at room temperature for 1.5 h and then ether (1500 mL) was added. The supernatant was decanted from the resulting black gum, and the insoluble residue was washed thoroughly with methylene chloride (3 × 250 mL). The combined organic solution were filtered through a pad of florisil to afford a light bright yellow clear solution. Solvents were removed *in vacuo* and the residue was purified by silica gel chromatography using methylene chloride as eluent to afford the title compound as a yellow solid (71%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.45 (d, J = 1.5 Hz, 1H), 8.28 (dd, J = 8.1, 1.5 Hz, 1H), 8.07 (d, J = 8.1 Hz, 1H). ^{13}CNMR (CD_3OD, 125 MHz) δ 187.7, 139.2, 134.2, 126.2, 125.7.

2-Benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-acrylic acid methyl ester

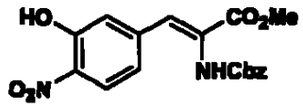


1,1,3,3-Tetramethylguanidine (41.2 mL, 329 mmol) was added at room temperature to a solution of N-(benzyloxycarbonyl)-alpha-phophonoglycine trimethyl ester (114.1g, 344 mmol) in tetrahydrofuran (800 mL). The mixture was stirred at room temperature for 15 min and cooled to –78°C. A solution 3,4-dinitro-benzaldehyde (61.4 g, 313 mmol) in tetrahydrofuran (200 mL) was slowly added via cannula. The resulting mixture was stirred at –78°C for 2h and then allowed to warm to room temperature overnight. Solvents were removed *in vacuo*, and the yellow residue was dissolved in 4.5 L of ethyl acetate. The solution was washed with 1.5 L of 1N sulfuric acid, water twice, brine and dried over sodium sulfate. After filtration, solvents were removed *in vacuo* and the residue was crystallized from ethyl acetate

(20 g crude product/100 mL of ethyl acetate). The yellow crystals were collected and further purified by chromatography on silica gel using methylene chloride as eluent. The title compound was obtained a s yellow crystals (77%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.85 (d, J = 1.5 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.5, 1.5 Hz, 1H), 7.35 – 7.34 (m, 3H), 7.34 (br s, 2H), 7.23 (s, 1H), 6.95 (br s, 1H), 5.07 (s, 2H), 3.90 (s, 3H).

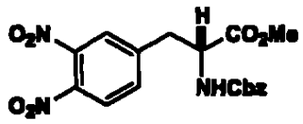
Similarly prepared:

2-Benzyloxycarbonylamino-3-(3-hydroxy-4-nitro-phenyl)-acrylic acid methyl ester



^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, J = 9.0 Hz, 1H), 7.32 (br s, sH), 7.28 (br s, 2H), 7.17 (s, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.01 (dd, J = 9.0, 2.0 Hz, 1H), 6.74 (br s, 1H), 5.06 (s, 2H), 3.86 (s, 3H).

(R)-2-Benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-propionic acid methyl ester

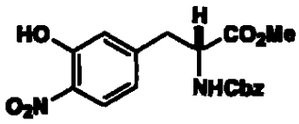


An oven-dried 500 mL Shlenck flask was put into a glove-bag filled with nitrogen. After the glove-bag was evacuated and filled with nitrogen (3x), the flask was sealed and taken out of the glove-bag and weighed. It was put back into the glove-bag and evacuated and filled with nitrogen (3x), then it was charged with (-)-1,2-bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadienene)rhodium (I) trifluoromethanesulfonate. The flask was sealed and taken out of the glove-bag and weighed (784 mg, 1.08 mmol). 2-Benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-acrylic acid methyl ester (8.72 g, 21.7 mmol) was added to another 500 mL of Schlenck flask and was evacuated and filled with nitrogen (3x). Methylene chloride (350 mL, degassed with nitrogen for 2 h) was added and the resulting solution was transferred to the catalyst flask via cannula. The flask was purged and filled with hydrogen (4x) and the mixture was stirred at room temperature for 4h. The solvents were removed *in vacuo* and the residue was purified by silica gel chromatography

using ethyl acetate/hexanes (1:1) as eluent to afford the title compound as a light tan gummy solid (99% yield and 99.2% ee determined by HPLC analysis using the following conditions: Chiralpak AD column (4.6 x 250 mm, 10 um; A = ethanol, B = hexane; 40% B @ 1.0 mL/min for 14 min; retention times: 10.9 min for R enatiomer and 6.9 min for S enatiomer). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 – 7.31 (m, 5H), 5.37 (d, J = 6.0 Hz, 1H), 5.13 – 5.05 (m, 2H), 4.68 (d, J = 6.0 Hz, 1H), 3.71 (s, 3H), 3.36 (dd, J = 13.5, 5.0 Hz, 1H), 3.17 (dd, J = 13.5, 6.0 Hz, 1H).

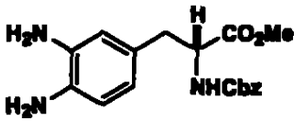
Similarly prepared:

(R)-2-Benzyloxycarbonylamino-3-(3-hydroxy-4-nitro-phenyl)-propionic acid methyl ester



^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 9.0 Hz, 1H), 7.36 – 7.30 (m, 5H), 6.90 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 5.29 (d, j = 7.0 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.68 (dd, j = 13.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.20 (dd, j = 13.5, 5.0 Hz, 1H), 3.05 (dd, J = 13.5, 6.0 Hz, 1H).

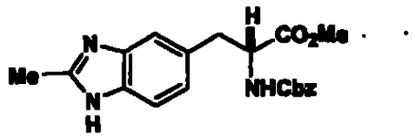
(R)-2-Benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester



Solid ammonium formate (2.27 g, 36 mmol) was added in small portions at 0°C to a methanol (50 mL, degassed with nitrogen for 2 h) suspension of (R)-2-benzyloxycarbonylamino-3-(3,4-dinitro-phenyl)-propionic acid methyl ester (1.45 g, 3.6 mmol) and zinc powder (1.41 g, 21.6 mmol). The resulting mixture was stirred at room temperature overnight. The solvents were removed *in vacuo* and then toluene (30 mL, degassed) and ethyl acetate (30 mL, degassed) were added, followed by acetic acid (3 mL). The mixture was further diluted until all organic solids dissolved, then it was washed with water, brine and dried over sodium sulfate. After filtration,

solvents were removed *in vacuo* to afford the title compound containing 1 equivalent of acetic acid as a reddish gummy solid (85%). Mass Spec.: 344.18 $(MH)^+$.

(R)-2-Benzyloxycarbonylamino-3-(2-methyl-1H-benzoimidazol-5-yl)-propionic acid methyl ester

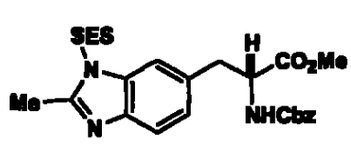


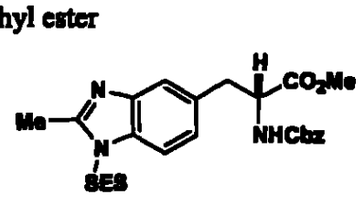
A solution of (R)-2-benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester-acetic acid (640 mg) in acetic acid (8 mL) was heated at 130°C for 4h. The mixture was then poured into water and cooled to 0°C. The pH was adjusted to 8 by gradual addition of solid sodium bicarbonate. The mixture was then extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with water, brine and dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a browniah foamy solid (95%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.26 – 7.22 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 5.03 (d, J = 12.5 Hz, 1H), 4.99 (d, J = 13.0 hz, 1H), 4.51 (dd, J = 8.5, 5.5 Hz, 1H), 3.70 (s, 3H), 3.27 (dd, J = 13.5, 5.0 Hz, 1H), 3.03 (dd, J = 14.0, 9.0 Hz, 1H), 2.55 (s, 3H). Mass spec.: 368.19 $(MH)^+$.

(R)-2-Benzyloxycarbonylamino-3-[2-methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-propionic acid methyl ester

and

(R)-2-Benzyloxycarbonylamino-3-[2-methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-propionic acid methyl ester





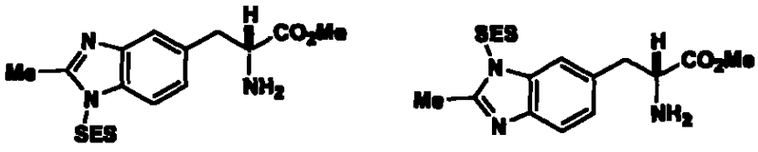
To a suspension of (R)-2-benzyloxycarbonylamino-3-(2-methyl-1H-benzoimidazol-5-yl)-propionic acid methyl ester (533 mg, 1.96 mmol), and sodium carbonate in acetonitrile (20 mL) was added neat 2-trimethylsilanyl-ethanesulfonyl chloride all at once. The mixture was stirred at room temperature overnight.

Solvents were removed and the residue was purified by chromatography on silica gel using ethyl acetate/hexanes (1:2) as eluent to afford the title compound as a waxy solid (1:1 mixture of N1 and N3 isomers, 66%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.68 (d, J = 8.5 hz, 0.5H), 7.55 (d, J = 8.5 Hz, 0.5 H), 7.53 (s, 0.5H), 7.41 (s, 0.5 H), 7.34 – 7.29 (m, 5H), 7.06 – 7.04 (m, 1H), 5.22 (d, J = 8.0 Hz, 0.5 H), 5.17 (d, J = 7.5 Hz, 0.5 H), 5.11 – 5.07 (m, 2H), 4.72 – 4.69 (m, 1H), 3.75 (s, 1.5 H), 3.72 (s, 1.5 H), 3.24 – 3.17 (m, 2H), 2.79 (s, 3H), 0.92 – 0.83 (m, 2H), -0.02 (s, 4.5 H), -0.05 (s, 4.5H). Mass spec.: 532.26 $(MH)^+$.

(R)-2-Amino-3-[2-methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-propionic acid methyl ester

and

(R)-2-Amino-3-[2-methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-propionic acid methyl ester



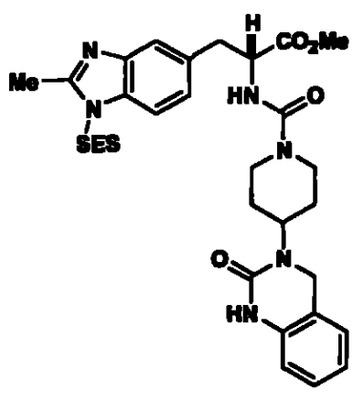
A methanol (50 mL) suspension of (R)-2-benzyloxycarbonylamino-3-[2-methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-propionic acid methyl ester and (R)-2-Benzyloxycarbonylamino-3-[2-methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-propionic acid methyl ester (1:1 mixture, 600 mg), and 10% palladium on charcoal (180 mg) was agitated on a Parr apparatus overnight under 40 psi of hydrogen at room temperature. After replacing the hydrogen atmosphere with nitrogen, the mixture was filtered through a pad of celite. Solvents were removed *in vacuo* to afford the title compound as a tan solid (80%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.81 (d, J = 8.5, 0.5 Hz, 0.5 H), 7.70 (s, 0.5 H), 7.58 (d, J = 8.5 Hz, 0.5 H), 7.49 (s, 0.5 H), 7.25 (d, J = 9.0 Hz, 1H), 3.89 (dd, J = 14.0, 6.5 Hz, 1H), 3.75 (s, 1.5 H), 3.72 (s, 1.5 H), 3.55 – 3.51 (m, 2H), 3.18 (d, J = 6.0 Hz, 1H), 3.22 – 3.18 (m, 0.5 H), 3.14 – 3.09 (m, 0.5 H), 2.81 (s, 1.5 H), 2.80 (s, 1.5 H), 0.92 – 0.88 (m, 2H), 0.02 (s, 4.5 H), 0.01 (s, 4.5 H); ^{13}CNMR (CD_3OD, 125 MHz) δ 174.3, 174.1, 153.5, 153.3, 141.7, 140.6, 133.9, 133.82, 133.78, 132.7, 126.5, 126.3,

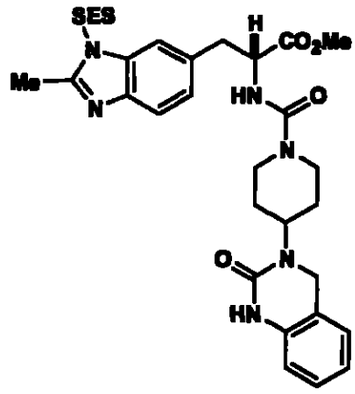
119.7, 119.0, 114.1, 113.4, 55.6, 51.8, 51.7, 51.6, 40.2, 39.8, 15.83, 15.77, 9.9, -3.07, -3.11. Mass spec.: 398.20 $(MH)^+$.

(R)-3-[2-Methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester

and

(R)-3-[2-Methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester

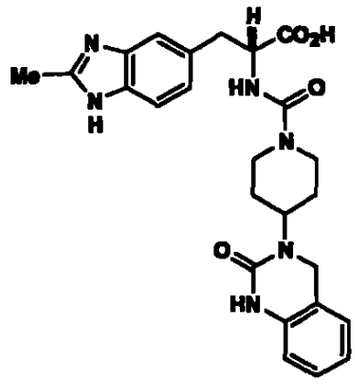




Prepared as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester. Purified by silica gel chromatography using ethyl acetate with 1% triethylamine as eluent to afford the title compound as an off-white solid (87%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.82 (d, J = 8.5 Hz, 0.5 H), 7.80 (s, 0.5 H), 7.59 (d, J = 8.0 Hz, 0.5 H), 7.55 (s, 0.5 H), 7.33 – 7.30 (m, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 4.60 – 4.55 (m, 1H), 4.45 – 4.40 (m, 1H), 4.29 – 4.27 (m, 2H), 4.15 – 4.10 (m, 2H), 3.77 (s, 1.5 H), 3.74 (s, 1.5 H), 3.56 – 3.51 (m, 2H), 3.35 – 3.31 (m, 2H), 3.21 – 3.15 (m, 1H), 2.91 – 2.80 (m, 2H), 2.78 (s, 1.5 H), 2.77 (s, 1.5 H), 1.76 – 1.73 (m, 1H), 1.66 – 1.61 (m, 2H), 0.92 – 0.87 (m, 2H), 0.009 (s, 4.5 H), -0.007 (s, 4.5 H). ^{13}CNMR (CD_3OD, 125 MHz) 173.8, 173.7, 158.2, 158.1, 155.6, 153.4, 153.2, 141.6, 140.3, 137.2, 135.3, 135.1, 133.7, 132.5, 128.2, 126.4, 126.3, 125.7, 122.13, 122.10,

119.6, 118.8, 118.4, 114.0, 113.4, 113.2, 57.3, 56.2, 51.9, 51.7, 51.5, 43.8, 43.7, 42.9, 37.6, 37.2, 28.4, 17.4, 15.7, 15.6, 9.9, -3.1, -3.2. Mass spec.: 655.36 $(MH)^+$.

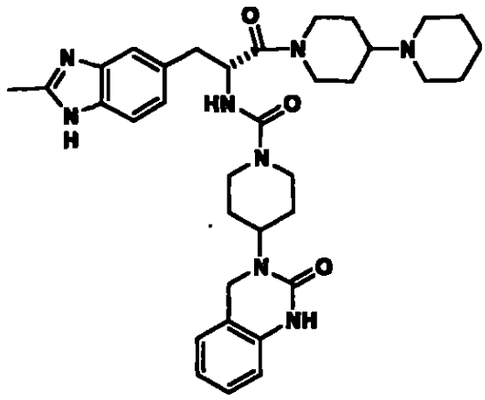
(R)-3-(2-Methyl-1H-benzoimidazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



The 1:1 mixture of (R)-3-[2-Methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-1H-benzoimidazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester and (R)-3-[2-Methyl-3-(2-trimethylsilanyl-ethanesulfonyl)-3H-benzoimidazol-5-yl]-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester was treated as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid. The hydrolysis conditions (lithium hydroxide/methanol-tetrahydrofuran-water (1:1:1) at –15 °C overnight were used. The title compound was obtained as a white solid (25%). Mass spec.: 477.24 $(MH)^+$.

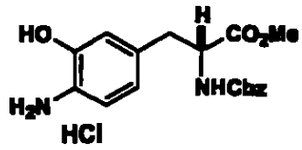
Example 46

(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(2-methyl-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. Purified by silica gel chromatography using methylene chloride:methanol:triethylamine (93:5:2) as eluent to give a white solid. This was dissolved in ethyl acetate (60 mL) and washed with a 1:1 sat. sodium bicarbonate/brine twice and dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a white solid (11% yield). LC/MS: t_R = 1.59 min, 627.34 $(MH)^+$.

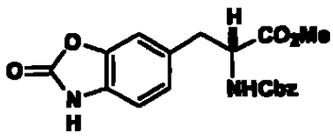
(R)-3-(4-Amino-3-hydroxy-phenyl)-2-benzyloxycarbonylamino-propionic acid methyl ester hydochloride



Powdered iron (3.7 g, 66.4 mmol) and ammonium chloride (5.9 g, 111 mmol) were added at 0°C to a solution of (R)-2-benzyloxycarbonylamino-3-(3-hydroxy-4-nitro-phenyl)-propionic acid methyl ester (2.07 g, 5.53 mmol) in degassed 1:1 methanol/water (400 mL). The resulting mixture was stirred at room temperature for 48 h. Trifluoroacetic acid (7 mL) was added, and the mixture was swirled until it was a clear dark red solution containing a suspension of unreacted iron powder. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was extracted with ethyl acetate (2 × 150 mL), the combined organic layers were washed with brine and dried over sodium sulfate. After filtration, hydrochloric acid (4.2 mL, 4M in dioxane) was added. Solvents were removed *in vacuo*, and the title compound

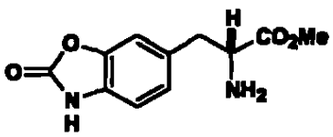
was obtained as a tan foamy solid (80%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.34 – 7.28 (m, 5H), 7.20 (d, J = 8.0 hz, 1H), 6.88 (s, 1H), 6.78 (d, J = 7.5 Hz, 1H), 5.05 – 5.00 (m, 2H), 4.42 (dd, J = 8.5, 5.0 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 1H), 3.33 (br s, 2H), 3.11 (dd, J = 14.0, 5.0 hz, 1H), 2.90 (dd, J = 13.5, 9.0 Hz, 1H). ^{13}CNMR (CD_3OD, 125 MHz) 172.5, 157.4, 151.2, 140.2, 137.0, 128.5, 128.0, 127.7, 123.8, 120.9, 117.0, 116.9, 67.2, 55.7, 52.0, 37.2. Mass spec.: 345.20 $(MH)^+$.

(R)-2-Benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



A methylene chloride (15 mL) solution of carbonyl diimidazole (498 mg, 3.07 mmol) was added at 0°C to a solution of (R)-3-(4-amino-3-hydroxy-phenyl)-2-benzyloxycarbonylamino-propionic acid methyl ester (1.17g, 3.07 mmol), diisopropylethylamine (1.60 mL, 9.21 mmol), and methylene chloride (85 mL). The mixture was stirred at 0°C for 4 h. The solvents were removed *in vacuo* and the residue was purified by silica gel chromatography using ethyl acetate/hexanes as eluent to afford the title compound as a white solid (51%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.07 (s, 1H), 7.37 – 7.29 (m, 5H), 6.96 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.36 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 4.65 (dd, J = 13.5, 5.5 Hz, 1H), 3.74 (s, 3H), 3.17 (dd, J = 14.0, 5.5 Hz, 1H), 3.07 (dd, J = 14.0, 6.0 Hz, 1H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ 171.9, 155.7, 155.5, 144.1, 136.2, 130.8, 128.6, 128.42, 128.38, 128.2, 125.1, 111.1, 109.8, 67.2, 55.1, 52.6, 38.3. Mass spec.: 371.18 $(MH)^+$.

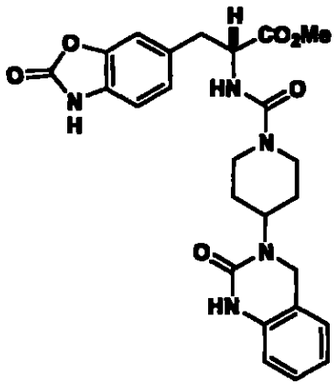
(R)-2-Amino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



A solution of (R)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (310 mg) in 4.4% formic acid in

methanol (20 ml, freshly prepared in degassed methanol) was added via cannula to a suspension of 10% palladium on charcoal in 4.4% formic acid in methanol (20 ml, freshly prepared in degassed methanol). The resulting mixture was stirred at room temperature for 4 h. After filtration through a pad of celite, the solvents were removed *in vacuo* giving a tan solid. The solid was dissolved in a mixture of ethyl acetate (50 mL), toluene (10 mL) and ethanol (40 ml), and solid sodium bicarbonate (3.1 g) was added. The mixture was stirred at room temperature for 2h and filtered. Solvents were removed *in vacuo* to afford the title compound. ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.41 (br s, 2H), 7.17 (s, 1H), 7.09 (br s, 2H), 4.32 (s, 1H), 3.83 (s, 3H), 3.33 (s, 1H), 3.30 (s, 1H), 3.22 (s, 1H). Mass spec.: 237.20 $(MH)^+$.

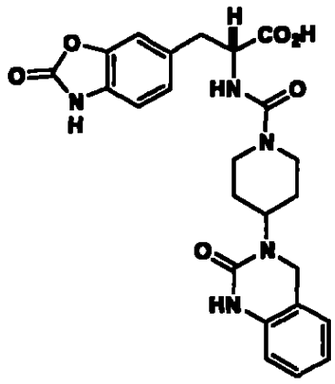
(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



Prepared as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester. Purified by silica gel chromatography using methylene chloride:methanol:triethylamine (93:5:2) as eluent to afford the title compound as a white solid (33%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.17 – 7.13 (m, 3H), 7.08 (d, J = 7.9 hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.55 – 4.51 (m, 1H), 4.44 – 4.41 (m, 1H), 4.33 (s, 2H), 4.14 – 4.10 (m,2H), 3.74 (s, 3H), 3.33 (br s, 2H), 3.23 (dd, j = 13.7, 5.2 Hz, 1H), 3.03 (dd, J = 14.0, 9.7 Hz, 1H), 2.92 – 2.82 (m, 2H), 1.79 – 1.63 (m, 4H). ^{13}CNMR (CD_3OD, 125 MHz) 173.8, 158.2, 156.2, 155.6, 144.4, 137.1, 132.7, 129.3, 128.2, 125.7, 125.0, 122.2, 118.4, 113.4, 110.6, 109.6, 56.2, 52.0, 51.7, 43.8, 42.9, 37.3, 28.4. Mass spec.: 494.30 $(MH)^+$.

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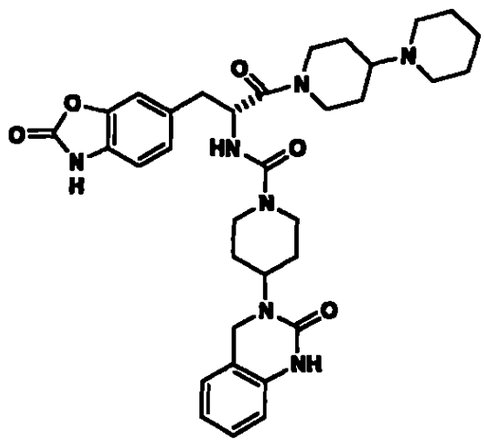
(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



Prepared as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid. The hydrolysis conditions (lithium hydroxide/methanol-tetrahydrofuran-water (1:1:1) at –15°C overnight were used. The title compound was obtained as a white solid (95%). Mass spec.: 480.30 $(MH)^+$.

Example 47

(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide

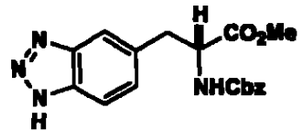


Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-

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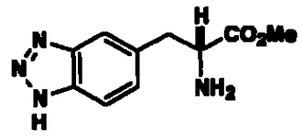
trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. The crude product was purified by silica gel chromatography using methylene chloride:methanol:triethylamine (93:5:2) as eluent to give a white solid. This was dissolved in ethyl acetate (60 mL) and washed with a 1:1 sat. sodium bicarbonate/brine twice and dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a white solid (70%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.20 – 7.14 (m 4H), 7.08 (d, J = 9.0 Hz, 1H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.99 – 4.94 (m, 1H), 4.61 – 4.58 (m, 1H), 4.47 – 4.43 (m, 1H), 4.39 (s, 1H), 4.23 – 4.16 (m, 2H), 4.08 – 4.04 (m, 1H), 3.06 – 2.88 (m, 5H), 2.74 – 2.69 (m, 2H), 2.59 – 2.52 (m, 2H), 2.41 – 2.33 (m, 2H), 1.96 – 1.89 (m, 1H), 1.88 – 1.47 (m, 16H). LC/MS: t_R = 1.86 min, 630.31 $(MH)^+$.

(R)-3-(1H-Benzotriazol-5-yl)-2-benzyloxycarbonylamino-propionic acid methyl ester



To a solution of (*R*)-2-benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester mono acetate (2.68 g, 6.65 mmol) in acetic acid (30 mL) and water (40 mL), at room temperature was added a solution of sodium nitrite (0.46 g, 6.65 mmol) in water (8 mL), dropwise over several minutes. The resulting mixture was stirred at room temperature for 20 min, then cooled to 0°C, concentrated ammonium hydroxide was added to adjust pH to 11. The mixture was extracted with ethyl acetate twice in the presence of solid sodium chloride, and the organic layers were dried over sodium sulfate. After filtration, solvents were removed *in vacuo* and the residue was purified by chromatography on silica gel using ethyl acetate/hexanes (6:4) as eluent to afford the title compound as a tan solid (94% yield). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.75 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.31 – 7.25 (m, 5H), 7.18 (d, J = 8.5 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.74 (dd, j = 13.5, 6.0 Hz, 1H), 3.73 (s, 3H), 3.34 (dd, J = 14.0, 5.5 Hz,1H), 3.22 (dd, J = 13.5, 6.0 Hz, 1H). ^{13}CNMR (CD_3OD, 125 MHz) δ 172.1, 156.0, 136.1, 128.6, 128.3, 128.1, 67.2, 55.2, 52.7, 38.5. Mass spec. 355.18 $(MH)^+$.

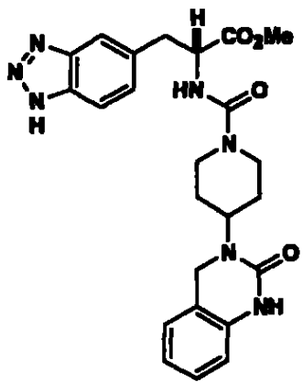
(R)-2-Amino-3-(1H-benzotriazol-5-yl)-propionic acid methyl ester



Prepared as described above for (R)-2-amino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.38 (br s, 2H), 7.89 (d, J = 7.5 Hz, 1H), 7.81 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 4.44 (s, 1H), 3.81 (s, 3H), 3.48 – 3.45 (m, 1H), 3.40 – 3.37 (m, 1H), 3.33 (br s, 1H). ^{13}CNMR (CD_3OD, 125 MHz) δ 169.8, 139.4, 138.9, 133.0, 127.6, 115.52, 115.47, 54.3, 52.6, 36.7. Mass spec. 221.15 $(MH)^+$.

Example 48

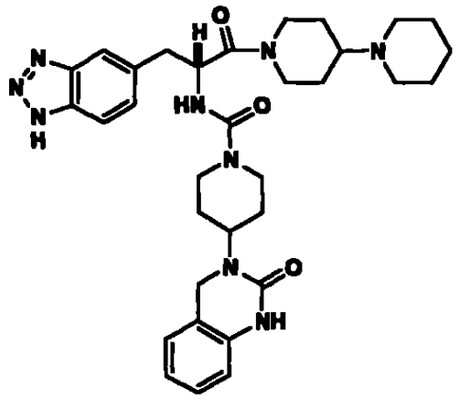
(R)-3-(1H-Benzotriazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



Prepared as described above for (*R*)-2-{[4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-yl]-propionic acid methyl ester except that carbonyl diimidazole was used in place of *N,N*-disuccinimidyl carbonate (DSC). ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.82 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.39 (dd, J = 8.7, 1.2 Hz, 1H), 7.15 – 7.08 (m, 2H), 6.94 (td, J = 7.5, 0.9 Hz, 1H), 6.75 (d, J = 7.8 Hz,1H), 4.67 – 4.60 (m, 1H), 4.39 – 4.31 (m, 1H), 4.15 (s, 2H), 4.08 – 4.03 (m, 2H), 3.72 (s, 3H), 3.38 (dd, J = 13.9, 5.5 Hz, 1H), 3.32 – 3.29 (m, 1H), 3.17 (dd, J = 13.9, 10.3 Hz, 1H), 2.87 – 2.71 (m, 2H), 1.64 – 1.48 (m, 4H). Mass spec. 478.30 $(MH)^+$.

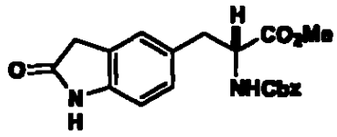
Example 49

(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(1H-benzotriazol-5-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide



Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. Purified by silica gel chromatography using methylene chloride/methanol/triethylamine (93:5:2) as eluent. ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.83 d, J = 8.2 Hz, 0.75H), 7.79 (d, J = 8.5 Hz, 0.25H), 7.71 (s, 0.25H), 7.69 (s, 0.75H), 7.33 (d, J = 9.2 Hz, 1H), 7.16 – 7.12 (m, 2H), 6.96 – 6.91 (m, 1H), 6.78 (d, J = 8.0 Hz, 0.75H), 6.77 (d, J = 8.0 Hz, 0.25H), 5.07 – 5.03 (m, 1H), 4.58 – 4.55 (m, 1H), 4.45 – 4.40 (m, 1H), 4.34 (s, 1.25H), 4.24 (s, 0.75H), 4.20 – 4.05 (m, 2.25H), 4.00 – 3.96 (m, 0.75H), 3.24 – 3.09 (m, 2H), 2.91 – 2.78 (m, 4H), 2.64 – 2.61 (m, 2H), 2.56 – 2.42 (m, 2H), 2.15 – 2.10 (m, 1.25H), 2.02 – 1.98 (m, 1.75H), 1.95 – 1.90 (m, 1H), 1.68 – 1.60 (m, 8H), 1.54 – 1.46 (m, 6H). LC/MS: t_R = 1.86 min, 614.28 $(MH)^+$.

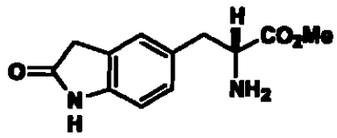
(R)-2-Benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-1H-indol-5-yl)-propionic acid methyl ester



$PyHBr_3$ (1.28 g, 4.02 mmol) was added in small portions over 30 min to a solution of (R)-2-benzyloxycarbonylamino-3-(1*H*-indol-5-yl)-propionic acid methyl ester (0.47 g, 1.34 mmol) in *t*-butanol (10 mL) while the reaction temperature was maintained between 25-30°C. The resulting mixture was stirred at room temperature

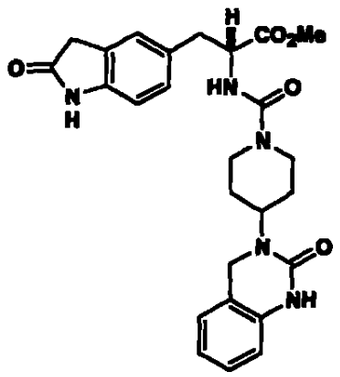
for 3.5 h. The solvent was removed *in vacuo*, and the residue was extracted with ethyl acetate (2x). The combined organic phases were washed with brine and dried over sodium sulfate. After filtration, solvents were removed and the residue was azeotropically dried with anhydrous ethanol. The residue was dissolved in glacial acetic acid (10 mL) and zinc powder (0.88 g, 13.4 mmol) was added. The mixture was stirred at room temperature overnight. After the acetic acid was removed *in vacuo*, the residue was purified by flash chromatography on silica gel using ethyl acetate/hexanes [(1:3) first and then (3:2)] as eluent to afford the title compound as a white solid (41% for 2 steps). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 8.03 (s, 1H), 7.36 – 7.31 (m, 5H), 6.94 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 5.26 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 5.05 (d, j = 12.5 Hz, 1H), 4.61 (dd, J = 13.5, 6.0 hz, 1H), 3.72 (s, 3H), 3.45 (s, 2H), 3.10 (dd, J = 14.0, 5.5 Hz, 1H), 3.00 (dd, J = 14.0, 6.0 Hz, 1H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ 177.7, 172.2, 155.7, 141.7, 136.3, 129.8, 128.9, 128.6, 128.3, 128.2, 125.8, 125.6, 109.8, 67.1, 55.1, 52.5, 38.0, 36. Mass spec. 369.20 $(MH)^+$.

(R)-2-Amino-3-(2-oxo-2,3-dihydro-1H-indol-5-yl)-propionic acid methyl ester



Prepared as described above for (R)-2-amino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. ^{1}H-NMR (CD_3OD, 500 MHz) δ 8.48 (br s, 2H), 7.16 (s, 1H), 7.10 (s, 1H), 6.89 (s, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 3.54 (s, 1H), 3.33 (s, 2H), 3.20 (s, 1H), 3.12 (s, 1H). ^{13}CNMR (CD_3OD, 125 MHz) δ 178.9, 170.7, 143.3, 129.0, 128.6, 126.9, 125.6, 110.0, 57.3, 54.6, 52.3, 37.0. Mass spec. 235.30 $(MH)^+$.

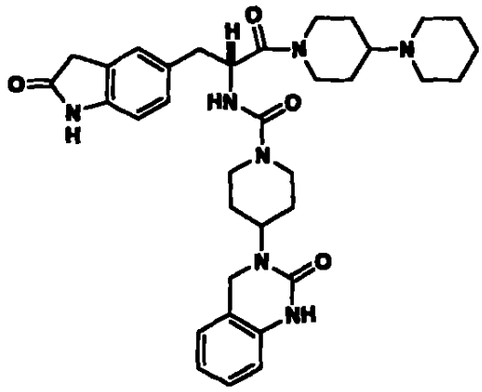
(R)-3-(2-Oxo-2,3-dihydro-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A solution of phosgene in toluene (2M, 0.158 mL, 0.30 mmol) was added to a vigorously stirred mixture of (*R*)-2-amino-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)-propionic acid methyl ester (70 mg, 0.25 mmol) in methylene chloride (15 mL) and saturated sodium bicarbonate (7.5 mL). After the mixture was stirred at room temperature for 30 min, 3-piperidin-4-yl-3,4-dihydro-1*H*-quinazolin-2-one (58 mg, 0.25 mmol) was added. The resulting mixture was stirred at room temperature for 1.5 h, diluted with ethyl acetate, and washed with 0.25 N hydrochloric acid that had been saturated with solid sodium chloride. The organic layers were dried over sodium sulfate. After filtration, solvents were removed to afford the title compound as a tan viscous oil. LC/MS: $t_R = 2.01$ min, 492.10 $(MH)^+$.

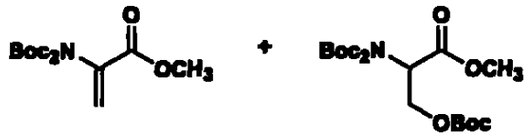
Example 50

(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(2-oxo-2,3-dihydro-1H-indol-5-ylmethyl)-ethyl]-amide



Prepared as described above for (*R*)-4-(2-oxo-1,4-dihydro-2*H*-quinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-[1-(2-trimethylsilanyl-ethanesulfonyl)-1*H*-indazol-5-ylmethyl]-ethyl}-amide. Purified by flash chromatography on silica gel using methylene chloride/methanol/triethylamine (93:5:2) as eluent. ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.20 – 7.09 (m, 4H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 0.65 H), 6.84 (d, *J* = 7.6 Hz, 0.35 H), 6.80 (d, *J* = 7.7 Hz, 1H), 5.51 (s, 0.65 H), 5.23 (s, 0.35 H), 4.99 – 4.95 (m, 0.65 H), 4.92 – 4.88 (m, 0.35 H), 4.60 – 4.56 (m, 1.65 H), 4.46 – 4.41 (m, 1.35 H), 4.39 (s, 1.3 H), 4.36 (s, 0.7 H), 4.24 – 4.17 (m, 2H), 4.05 – 4.02 (m, 1H), 3.65 – 3.61 (m, 2H), 3.52 – 3.47 (m, 1H), 3.20 – 3.16 (m, 1H), 3.00 – 2.88 (m, 2H), 2.70 – 2.64 (m, 2H), 2.53 – 2.46 (m, 2H), 2.40 – 2.34 (m, 2H), 1.94 – 1.46 (m, 15H), 1.39 – 1.36 (m, 2H). LC/MS: t_R = 1.83 min, 628.40 $(MH)^+$.

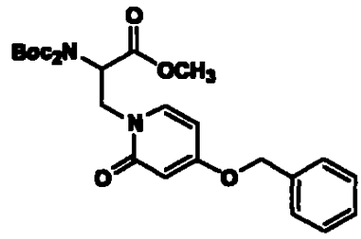
2-(Di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester



To a solution of 2-*tert*-butoxycarbonylamino-3-hydroxy-propionic acid methyl ester (10.0 g, 39 mmol) and di-*tert*-butyl-dicarbonate (21.8 g, 2.6 equiv.) in acetonitrile (40 mL) was added 4-dimethylaminopyridine (0.48 g, 0.1 equiv) at room temperature. The solution was stirred overnight and concentrated. The residue was dissolved in diethyl ether, washed sequentially with 1 M potassium hydrogen sulfate (2x), saturated sodium bicarbonate, brine, dried over magnesium sulfate, and concentrated to give 15.6 g (quant.) as an oil. Inspection of the ^{1}H NMR showed a mixture of the title compound and 2-(di-*tert*-butoxycarbonylamino)-3-*tert*-butoxycarbonyloxy-propionic acid methyl ester. As it was later found that both react with secondary amines to give the same products, the mixture was used without separation. 2-(Di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester: ^{1}H-NMR ($CDCl_3$) δ 1.45 (s, 18H), 3.78 (s, 3H), 5.63 (s, 1H), 6.33 (s, 1H). Mass spec.: 324.14 $(M+Na)^+$. 2-(Di-*tert*-butoxycarbonylamino)-3-*tert*-butoxycarbonyloxy-propionic acid methyl ester: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 1.49 (s, 18H), 3.72 (s,

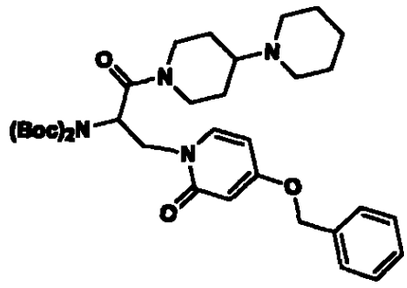
3H), 4.42 (dd, *J*=11.6, 9.2, 1H), 4.75 (dd, *J*=11.3, 4.6, 1H), 5.30 (dd, *J*=9.2, 4.6, 1H). Mass spec.: 442.21 $(M+Na)^+$.

(±)-3-(4-Benzyloxy-2-oxo-2H-pyridin-1-yl)-2-(di-*tert*-butoxycarbonylamino)-propionic acid methyl ester



To a solution of 2-(di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester (900 mg, 3.0 mmol), and 4-benzyloxy-1H-pyridin-2-one (630 mg, 1.03 equiv) in acetonitrile (2.5 mL) was added cesium carbonate (100 mg, 0.10 equiv). The resulting suspension was heated to 80°C via microwave for 2 h. The reaction was concentrated, dissolved in water, and extracted with methylene chloride (3x). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated to give 1.47 g (97%) which was used without purification. Mass spec.: 503.56 $(MH)^+$.

(±)-4-Benzyloxy-1-[3-[1,4']bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-oxo-propyl]-1H-pyridin-2-one



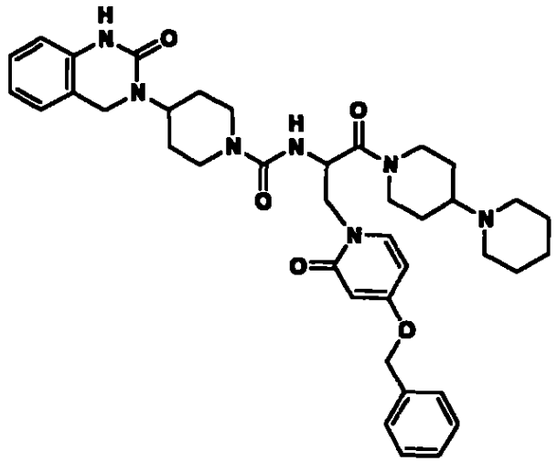
To a stirred solution of 3-(4-benzyloxy-2-oxo-2H-pyridin-1-yl)-2-(di-*tert*-butoxycarbonylamino)-propionic acid methyl ester (1.47 g, 2.9 mmol) in methanol (17 mL) was added a solution of lithium hydroxide monohydrate (0.50 g, 4 equiv) in water (2.85 mL). The reaction mixture was stirred for 3 h at room temperature, cooled to 0°C, treated with concentrated hydrochloric acid (0.99 mL), and

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concentrated to afford the crude acid, half of which was taken on in the following step. The crude acid was dissolved in methylene chloride (6 mL), cooled to 0°C and treated sequentially with 4-piperidyl-piperidine (0.25 g, 1 equiv), triethylamine (0.31 mL, 2.5 equiv), and bis-2-oxo-3-oxazolidinyl)phoshinic chloride (0.38 g, 1 equiv). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was concentrated, and purified by Prep HPLC to afford 489 mg (52%, 2 steps). Mass spec.: 639.41 $(MH)^+$.

Example 51

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-benzyloxy-2-oxo-2H pyridin-1-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide

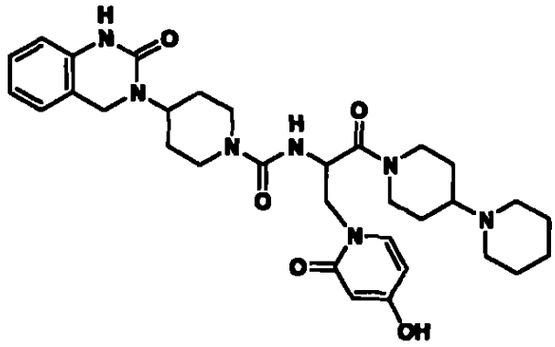


To a stirred solution of 4-benzyloxy-1-[3-[1,4']bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-oxo-propyl]-1H-pyridin-2-one in methylene chloride (3 mL) was added trifluoroacetic acid (1 mL) at 0°C. After 2 h, the reaction was concentrated to afford the crude amine (151 mg, 97%) as its trifluoroacetic acid salt [Mass spec.: 439.61 $(MH)^+$] which was split into two portions, using half in the following procedure. To a solution of the crude amine (75 mg, 0.11 mmol) and diisopropylethylamine (80 µL, 4 equiv) in methylene chloride (3 mL) at 0°C was added carbonyl diimidazole (29 mg, 1.6 equiv, in 2 portions). After stirring for 10 min, the solution was treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-acetic acid (40 mg, 1.15 equiv). The reaction was warmed to room temperature and stirred overnight. The reaction was concentrated and purified by prep TLC to give

40.8 mg (53%). ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.25-1.56 (m, 4H), 1.56-1.84 (m, 9H), 1.90-2.08 (m, 2H), 2.60-2.95 (m, 8H), 3.11 (dd, *J*=24.1, 12.8, 1H), 3.89 (ddd, *J*=22.0, 13.2, 9.2, 1H), 4.10 (dd, *J*=14.3, 14.1, 2H), 4.27-4.54 (m, 5H), 4.60 (bd, *J*=11.9, 1H), 5.08 (dd, *J*=13.2, 12.2, 2H), 5.26 (ddd, *J*=9.4, 9.4, 4.8, 1H), 6.05 (dd, *J*=13.7, 2.7, 1H), 6.16 (m, 1H), 6.77 (d, *J*=8.0, 1H), 6.84 (ddd, *J*=7.6, 7.6, 2.1, 1H), 7.04 (d, *J*=7.6, 1H), 7.12 (dd, *J*=7.6, 7.4, 1H), 7.28-7.43 (m, 5H), 7.48 (d, *J*=7.6, 1H). Mass spec.: 696.85 $(MH)^+$.

Example 52

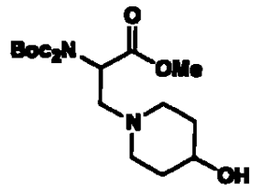
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-hydroxy-2-oxo-2H-pyridin-1-ylmethyl)-2-oxo-ethyl]-amide



A stirred solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-benzyloxy-2-oxo-2H-pyridin-1-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide (29 mg) and 10% palladium on charcoal (5 mg) in methanol (1 mL) was placed under an atmosphere of hydrogen. After 1 h at room temperature, the reaction was flushed with nitrogen, filtered through celite, and concentrated to give the product. ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.40-1.85 (*m*, 12H), 2.04 (dd, *J*=27.4, 17.0, 2H), 2.66 (dd, *J*=21.1, 11.0, 1H), 2.80-3.19 (m, 8H), 3.95 (ddd, *J*=49.8, 12.5, 7.9, 1H), 4.07-4.28 (m, 3H), 4.34 (bs, 2H), 4.36-4.59 (m, 2H), 4.63 (bd, *J*=12.8, 1H), 5.20 (m, 1H), 5.75 (dd, *J*=7.3, 2.1, 1H), 5.97 (dd, *J*=8.9, 7.6, 1H), 6.78 (d, *J*=7.6, 1H), 6.93 (dd, *J*=7.6, 7.3, 1H), 7.08-7.18 (m, 2H), 7.33 (dd, *J*=18.3, 11.0, 1H). Mass spec.: 606.32 $(MH)^+$.

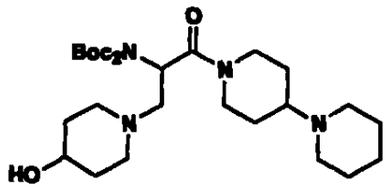
153

(±)-2-(Di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propionic acid methyl ester



To a solution of 2-(di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester (1.0 g, 3.0 mmol) in acetonitrile (10 mL) was added piperidin-4-ol (0.33 g, 1.1 equiv). A gentle stream of nitrogen was placed over the reaction while it stirred overnight. The crude oil which resulted was dissolved in ethyl acetate, washed with water, then brine, dried over magnesium sulfate, and concentrated to give 1.38 g (quant.) as an oil which was used without purification. Mass spec.: 403.42 $(MH)^+$.

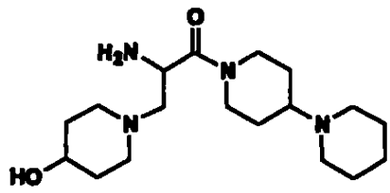
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propan-1-one



To a solution of 2-(di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propionic acid methyl ester (1.0 g, 2.5 mmol) in methanol (6 mL) was added a solution of lithium hydroxide monohydrate (400 mg, 3.9 equiv) in water (1 mL). The reaction was stirred 6 h, cooled to 0°C, neutralized with concentrated hydrochloric acid, and concentrated. The crude acid was used without purification. The crude acid was suspended in methylene chloride (25 mL), treated with a few drops of methanol to aid in dissolving the acid, and cooled to 0°C. The resulting suspension was treated sequentially with 4-piperidyl-piperidine (0.53 g, 1.25 equiv), triethylamine (0.70 mL, 2. equiv), and bis-2-oxo-3-oxazolidinyl)phoshinic chloride (0.80 g, 1.25 equiv). The reaction was allowed to warm to room temperature overnight. The reaction was concentrated and then purified by Prep HPLC to afford 310 mg (23%, 2 steps). Mass spec.: 539.49 $(MH)^+$.

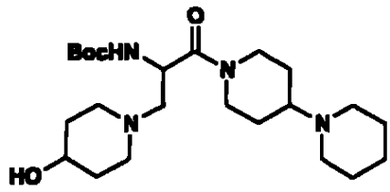
154

(±)-2-Amino-1-[1,4']bipiperidinyl-1'-yl-3-(4-hydroxy-piperidin-1-yl)-propan-1-one



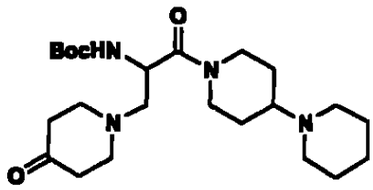
To a solution of 1-[1,4']bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propan-1-one (310 mg, 0.58 mmol) in methylene chloride (5 mL) at 0°C was added trifluoroacetic acid (2.0 mL). The ice bath was removed and the reaction stirred for 30 min. The reaction was concentrated to afford the product as its trifluoroacetic acid salt (400 mg, quant.) which was used without purification. Mass spec.: 339.46 $(MH)^+$.

(±)- [2-[1,4']Bipiperidinyl-1'-yl-1-(4-hydroxy-piperidin-1-ylmethyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester



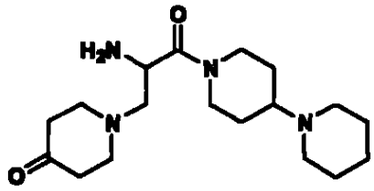
To a solution 2-amino-1-[1,4']bipiperidinyl-1'-yl-3-(4-hydroxy-piperidin-1-yl)-propan-1-one (trifluoroacetic acid salt, 300 mg, 0.58 mmol) and diisopropylethylamine (0.30 mL, 4 equiv) in tetrahydrofuran (5 mL) was added di-*tert*-butyl-dicarbonate (128 mg, 1 equiv). The resulting solution was stirred at room temperature for 1 h, and concentrated. The residue was dissolved in ethyl acetate, washed with water, then brine, dried over magnesium sulfate, and concentrated to afford to 248 mg (98%) which was used without purification. Mass spec.: 439.65 $(MH)^+$.

(±)- [2-[1,4']Bipiperidinyl-1'-yl-2-oxo-1-(4-oxo-piperidin-1-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester



To a solution of 1-[1,4']bipiperidinyl-1'-yl-2-(di-*tert*-butoxycarbonylamino)-3-(4-hydroxy-piperidin-1-yl)-propan-1-one (200 mg, 0.37 mmol) in methylene chloride (4 mL) was added Dess-Martin periodinane (316 mg, 2 equiv) in two portions. After 1 h, the reaction was quenched by the addition of saturated sodium bicarbonate, and extracted into methylene chloride (3x). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated to give 187 mg (94%) which was used without purification. Mass spec.: 437.63 $(MH)^+$.

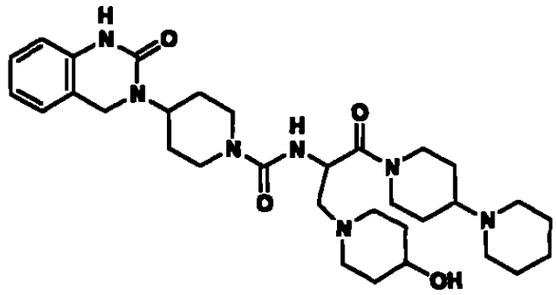
(±)-1-(2-Amino-3-[1,4']bipiperidinyl-1'-yl-3-oxo-propyl)-piperidin-4-one



To a solution of [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(4-oxo-piperidin-1-ylmethyl)-ethyl]-carbamic acid *tert*-butyl ester (100 mg, 0.23 mmol) in methylene chloride (5 mL) at 0°C was added trifluoroacetic acid. The ice bath was removed, stirring continued for 1 h, and the reaction concentrated to give 150 mg (96%) as its trifluoroacetic acid salt which was used without purification. Mass spec.: 337.64 $(MH)^+$.

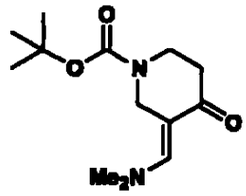
Example 53

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-hydroxy-piperidin-1-ylmethyl)-2-oxo-ethyl]-amide



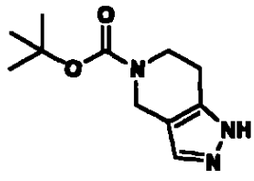
To a solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-hydroxy-piperidin-1-ylmethyl)-2-oxo-ethyl]-amide (3 trifluoroacetic acid salt, 200 mg, 0.39 mmol) in methylene chloride (5 mL) at 0°C was added diisopropylethylamine (0.27 mL, 3.9 equiv), and carbonyl diimidazole (63 mg, 1 equiv). After stirring for 15 min, the solution was treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (acetic acid salt, 142 mg, 1.25 equiv). The solution was warmed to room temperature and stirred overnight. The reaction was concentrated and purified by Prep TLC to give 130 mg (56%) as an oil. *LC/MS*: $t_R = 1.17$ min, 596.44 $(MH)^+$.

3-Dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester



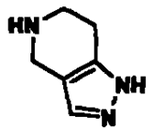
4-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester (10 g, 50 mmol) was dissolved in dimethyl formamide dimethylacetal (50 mL) and heated to reflux for 1.25 h. The solution was cooled, concentrated, and purified by flash chromatography to give 2.55 g (19%). Mass spec.: 255.16 $(MH)^+$.

1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester



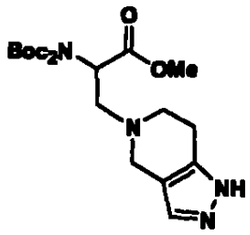
To a solution of 3-dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (2.55 g, 10 mmol) in methanol (50 mL) was added hydrazine hydrate (0.61 mL, 1.25 equiv). The solution was heated to reflux, immediately allowed to cool to room temperature, and concentrated to give 1.4 g (63%) which was used without purification. Mass spec.: 224.11 $(MH)^+$.

4,5,6,7-Tetrahydro-1H-pyrazolo[4,3-c]pyridine

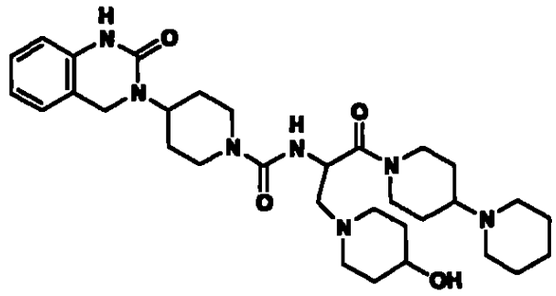


1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester (0.70 g, 3.1 mmol) was dissolved in trifluoroacetic acid (10 mL) at 0°C, stirred for 1 h, and was concentrated. The residue was dissolved in ethanol and treated with concentrated hydrochloric acid (1 mL). The bis-hydrochloride salt precipitated out as a white solid which was filtered to give 510 mg (83%). The free base was prepared as needed by dissolving the salt in water, loading it onto an SCX column, flushing with methanol, and then eluting with 2 M ammonia in methanol.

(±)-2-(Di-*tert*-butoxycarbonylamino)-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester

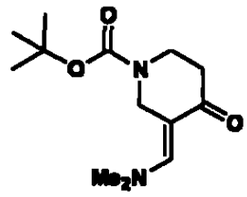


To a solution of 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (160 mg) in 2.5 mL methanol was added 2-(di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester (400 mg). The reaction was concentrated to approximately 1.5 mL by application of a gentle stream of nitrogen. The solution was stirred at room temperature overnight. The reaction was concentrated , dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was pure enough to use without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 2.73 (m, 3H), 2.91 (m, 1H), 3.06 (dd, *J*=13.4, 8.6, 1H), 3.22 (dd,



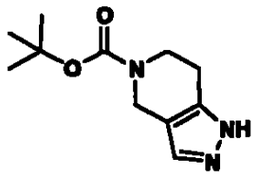
To a solution of 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-hydroxy-piperidin-1-ylmethyl)-2-oxo-ethyl]-amide (3 trifluoroacetic acid salt, 200 mg, 0.39 mmol) in methylene chloride (5 mL) at 0°C was added diisopropylethylamine (0.27 mL, 3.9 equiv), and carbonyl diimidazole (63 mg, 1 equiv). After stirring for 15 min, the solution was treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (acetic acid salt, 142 mg, 1.25 equiv). The solution was warmed to room temperature and stirred overnight. The reaction was concentrated and purified by Prep TLC to give 130 mg (56%) as an oil. LC/MS: $t_R = 1.17$ min, 596.44 $(MH)^+$.

3-Dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester



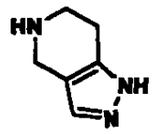
4-Oxo-piperidine-1-carboxylic acid *tert*-butyl ester (10 g, 50 mmol) was dissolved in dimethyl formamide dimethylacetal (50 mL) and heated to reflux for 1.25 h. The solution was cooled, concentrated, and purified by flash chromatography to give 2.55 g (19%). Mass spec.: 255.16 $(MH)^+$.

1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester



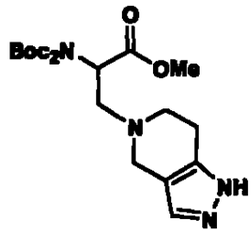
To a solution of 3-dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (2.55 g, 10 mmol) in methanol (50 mL) was added hydrazine hydrate (0.61 mL, 1.25 equiv). The solution was heated to reflux, immediately allowed to cool to room temperature, and concentrated to give 1.4 g (63%) which was used without purification. Mass spec.: 224.11 $(MH)^+$.

4,5,6,7-Tetrahydro-1H-pyrazolo[4,3-c]pyridine



1,4,6,7-Tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester (0.70 g, 3.1 mmol) was dissolved in trifluoroacetic acid (10 mL) at 0°C, stirred for 1 h, and was concentrated. The residue was dissolved in ethanol and treated with concentrated hydrochloric acid (1 mL). The bis-hydrochloride salt precipitated out as a white solid which was filtered to give 510 mg (83%). The free base was prepared as needed by dissolving the salt in water, loading it onto an SCX column, flushing with methanol, and then eluting with 2 M ammonia in methanol.

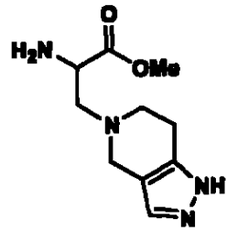
(±)-2-(Di-*tert*-butoxycarbonylamino)-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester



To a solution of 4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (160 mg) in 2.5 mL methanol was added 2-(di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester (400 mg). The reaction was concentrated to approximately 1.5 mL by application of a gentle stream of nitrogen. The solution was stirred at room temperature overnight. The reaction was concentrated, dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate, and concentrated. The resulting residue was pure enough to use without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 2.73 (m, 3H), 2.91 (m, 1H), 3.06 (dd, *J*=13.4, 8.6, 1H), 3.22 (dd,

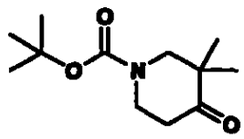
J=13.4, 8.2, 1H), 3.54 (d, J=13.4, 1H), 3.63 (d, J=13.4, 1H), 3.71 (s, 3H), 5.11 (dd, J=8.5, 5.2, 1H), 7.25 (s, 1H). Mass spec.: 425.23 $(MH)^+$.

(±)-2-Amino-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester



To a solution of 2-(di-*tert*-butoxycarbonylamino)-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester (0.55 g, 1 equiv.) in methylene chloride (5 mL, 0°C) was added trifluoroacetic acid (1.5 mL). The ice bath was removed and stirring continued for 2 h. The solution was concentrated, redissolved in methanol, and passed onto a column of strong cation exchange resin. After flushing with methanol, the product was removed from the column by eluting with 2 M ammonia in methanol to afford the product as its free base (275 mg, 95%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.71 (dd, J=12.8, 8.6, 1H), 2.74-2.91 (m, 6H), 3.48 (s, 2H), 3.54 (d, J=13.4, 1H), 3.62 (d, J=13.4, 1H), 3.69 (dd, J=8.2, 4.9, 1H), 3.73 (s, 3H), 7.27 (s, 1H). Mass spec.: 225.16 $(MH)^+$.

3,3-Dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester

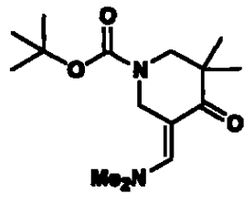


To a solution of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (16 g, 80 mmol) in tetrahydrofuran (400 mL) at 0°C was added sodium hydride (4.1 g, 2.1 equiv) in 4 portions. To this was added iodomethane (12.5 mL, 2.5 equiv) dropwise. The reaction was allowed to gradually warm to room temperature and stirred overnight. The reaction was concentrated, dissolved in diethyl ether, washed with brine, dried over magnesium sulfate, and concentrated. The product was crystallized from hot pentane (2X) to give 5.9 g (32%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.09 (s,

161

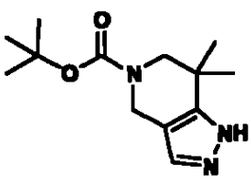
6H), 1.47 (s, 9H), 2.47 (dd, *J*=6.4, 6.4, 2H), 3.41 (m, 2H), 3.70 (m, 2H). Mass spec.: 250.12 $(M+Na)^+$.

5-Dimethylaminomethylene-3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester



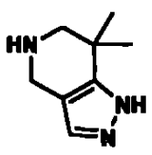
3,3-Dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (5 g, 22 mmol) was dissolved in dimethyl formamide dimethylacetal (25 mL) and heated at reflux for 2 h. The reaction mixture was then heated to 130°C for 1 h via microwave, and concentrated to give 6.43 g (quant.) as an oil which used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.07 (s, 6H), 1.45 (s, 9H), 3.06 (s, 6H), 3.37 (m, 2H), 4.57 (m, 2H), 7.41 (bs, 1H).

7,7-Dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester



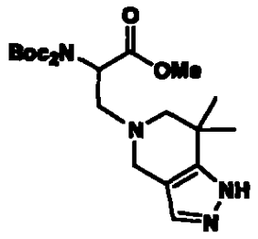
To a solution of 5-dimethylaminomethylene-3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (6.35 g, 22 mmol) in methanol (15 mL) was added hydrazine hydrate (1.2 mL, 1.1 equiv). The solution was stirred at room temperature overnight and concentrated to give 5.3 g (94%) which was used without purification. Mass spec.: 252.19 $(MH)^+$.

7,7-Dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine



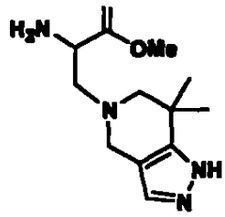
To a solution of 7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid *tert*-butyl ester (5.3 g, 21 mmol) in methylene chloride (10 mL) at 0°C was added trifluoroacetic acid (5 mL). The reaction was allowed to warm to room temperature, stirred 15 min, and treated with additional trifluoroacetic acid (5 mL). After 1 h, the reaction was concentrated, dissolved in ethanol (10 mL), cooled to 0°C, treated with concentrated hydrochloric acid (3 mL), and concentrated. The resulting solid was triturated with ethanol, and filtered to give 3.02 g (64%) as its bis-hydrochloride salt. The free base was prepared as needed by dissolving the salt in water, loading it onto an SCX column, flushing with methanol, and then eluting with 2M ammonia in methanol. ^{1}H-NMR (D_2O, 500 MHz) δ 1.49 (s, 6H), 3.46 (s, 2H), 4.39 (s, 2H), 7.86 (s, 1H). Mass spec.: 152.14 $(MH)^+$.

(±)-2-(Di-*tert*-butoxycarbonylamino)- 3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester



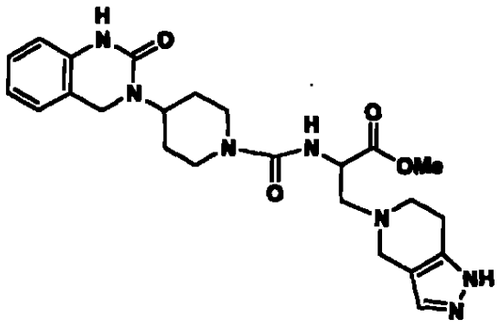
To a solution of 7,7-dimethyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (160 mg) in methanol (3 mL) was added 2-(di-*tert*-butoxycarbonylamino)-acrylic acid methyl ester (331 mg). A gentle stream of nitrogen was applied and the reaction stirred overnight. In the morning, the volume was greatly reduced. The last traces of solvent were removed under high vacuum to give 490mg (quant.) which was used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.24 (s, 3H), 1.26 (s, 3H), 1.38 (s, 18H), 2.33 (d, *J*=11.3, 1H), 2.57 (d, *J*=11.3, 1H), 3.09 (dd, *J*=13.1, 5.5, 1H), 3.15 (dd, *J*=13.4, 9.5, 1H), 3.35 (d, *J*=12.8, 1H), 3.57 (d, *J*=12.8, 1H), 3.68 (s, 3H), 5.13 (dd, *J*=9.5, 3.7, 1H), 7.16 (s, 1H). Mass spec.: 453.30 $(MH)^+$.

(±)-2-Amino-3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester



To a solution of 2-(di-*tert*-butoxycarbonylamino)- 3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester (0.49 g, 1 equiv) in methylene chloride (5 mL, 0°C) was added trifluoroacetic acid (1.5 mL). The ice bath was removed and stirring continued for 2 h. The solution was concentrated, redissolved in methanol, and loaded onto a column of strong cation exchange resin. After flushing with methanol, the product was removed from the column by eluting with 2M ammonia in methanol to afford the product as its free base (250 mg, 94%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.27 (s, 3H), 1.28 (s, 3H), 2.41 (d, *J*=11.3, 1H), 2.50 (d, *J*=11.3, 1H), 2.69 (dd, *J*=12.5, 7.9, 1H), 2.82 (dd, *J*=12.5, 5.2, 1H), 3.45 (d, *J*=12.8, 1H), 3.52 (d, *J*=12.8, 1H), 3.67 (m, 1H), 3.69 (s, 3H), 7.19 (s, 1H). Mass spec.: 253.16 $(MH)^+$.

(±)-2-{[4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester

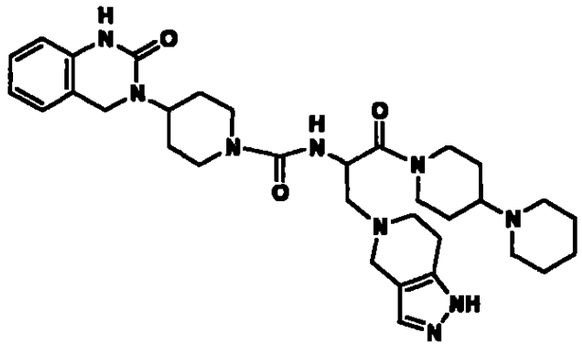


To a solution of 2-amino-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester (260 mg, 1 equiv) in methylene chloride (2 mL, 0°C) was added carbonyl diimidazole (188 mg, 1 equiv). After 15 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (295 mg, 1.1 equiv) was added in one portion. The ice bath was removed and stirring continued overnight. The reaction was concentrated and purified by column chromatography to give 118 mg (21%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.60-1.80 (m, 4H), 2.70-3.05 (m, 8H), 3.45 (s, 2H), 3.56 (d, *J*=13.4,

1H), 3.62 (d, *J*=13.4, 1H), 3.75 (s, 3H), 4.02 (d, *J*=13.1, 1H), 4.10 (d, *J*=12.5, 1H), 4.24 (s, 2H), 4.45-4.57 (m, 2H), 5.79 (bs, 1H), 6.68 (d, *J*=7.94, 1H), 6.90 (dd, *J*=7.3, 7.3, 1H), 7.00 (d, *J*=7.3, 1H), 7.13 (dd, *J*=7.6, 7.3, 1H), 7.25 (s, 1H), 7.82 (s, 1H). Mass spec.: 482.27 $(MH)^+$.

Example 54

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-ylmethyl)-ethyl]-amide

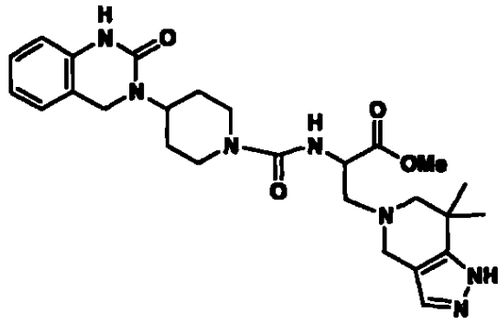


To a solution of 2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-3-(1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester (16 mg, 1 equiv) in methanol (0.6 mL) was added lithium hydroxide monohydrate (3 mg, 2.2 equiv) in water (0.1 mL) and stirred for 4 h at room temperature. The solution was cooled to 0°C, treated with aqueous 1 M potassium hydrogen sulfate (60 µl, 1.8 equiv), and concentrated to give the crude acid which was immediately used without purification. The crude acid was dissolved in dimethylformamide (0.3 mL) and sequentially treated with methylene chloride (0.15 mL), 4-piperidyl-piperidine (11 mg, 2 equiv), diisopropylethylamine (12 µL, 2 equiv), and PyBOP® (19 mg, 1.1 equiv). The solution was stirred 30 min and concentrated. The product was purified by column chromatography to give 17.6 mg (85%, 2 steps). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 9H), 1.62-1.78 (m, 5H), 1.81 (bd, *J*=11.0, 2H), 2.23-2.49 (m, 6H), 2.55-3.10 (m, 11H), 3.59 (d, *J*=7.3, 2H), 4.00-4.20 (m, 3H), 4.23 (s, 2H), 4.50 (m, 1H), 4.63 (m, 1H), 5.03 (m, 1H), 5.71 (d, *J*=7.3, 1H), 6.67 (d, *J*=7.9, 1H), 6.91 (dd, *J*=7.6, 7.3, 1H), 7.02 (dd, *J*=7.9, 7.3, 1H),

7.14 (dd, *J*=7.6, 7.6, 1H), 7.24 (s, 1H), 7.39 (s, 1H), 10.76 (bs, 1H). Mass spec.: 618.34 $(MH)^+$.

Example 55

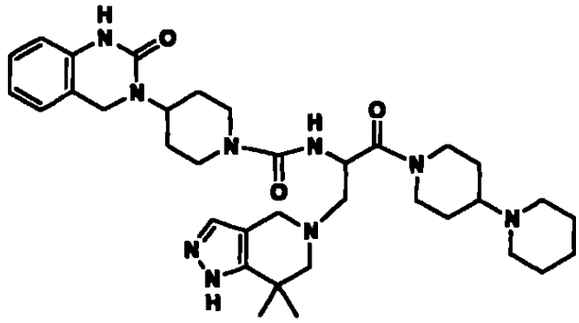
(±)-3-(7,7-Dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



To a solution of 2-amino-3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-propionic acid methyl ester (250 mg, 1 equiv) in tetrahydrofuran (4 mL, 0°C) was added carbonyl diimidazole (162 mg, 1 equiv). After 5 min, the ice bath was removed and the reaction stirred at room temperature for 30 min. To this was added 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (250 mg, 1.1 equiv) in one portion, and the reaction stirred overnight. The reaction was concentrated and purified by column chromatography to give 228 mg (45%). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 3H), 1.31 (s, 3H), 1:60-1.80 (m, 4H), 2.43 (d, *J*=11.6, 1H), 2.53 (d, *J*=11.3, 1H), 2.80-2.95 (m, 4H), 3.51 (dd, *J*=20.4, 13.1, 2H), 3.74 (s, 3H), 4.00 (d, *J*=13.7, 1H), 4.10 (d, *J*=12.2, 1H), 4.25 (dd, *J*=16.2, 14.4, 2H), 4.86 (m, 2H), 6.66 (d, *J*=7.6, 1H), 6.92 (dd, *J*=7.6, 7.3, 1H), 7.02 (d, *J*=7.3, 1H), 7.14 (dd, *J*=7.6, 7.6, 1H), 7.24 (s, 1H). Mass spec.: 510.27 $(MH)^+$.

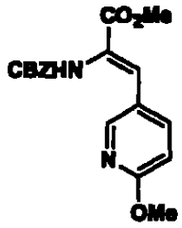
Example 56

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-ylmethyl)-2-oxo-ethyl]-amide



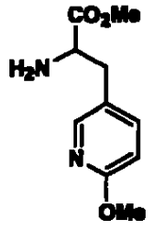
To a solution of 3-(7,7-dimethyl-1,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (20 mg, 1.0 equiv) in methanol (0.6 mL) was added lithium hydroxide monohydrate (4 mg, 2.2 equiv) in water (0.1 mL) and stirred for 4 h at room temperature. The solution was cooled to 0°C, treated with aqueous 1M potassium hydrogen sulfate (75 µl, 1.8 equiv), and concentrated to give the crude acid which was immediately used without purification. The crude acid was dissolved in dimethylformamide (0.3 mL) and sequentially treated with methylene chloride (0.15 mL), 4-piperidyl-piperidine (13 mg, 2 equiv), diisopropylethylamine (14 µL, 2 equiv), and PyBOP® (22 mg, 1.1 equiv). The solution was stirred 1.5 h and concentrated. The product was purified by column chromatography to give a product which was tainted with HOBT. The HOBT was removed by passing the product through a plug of basic alumina, eluting with 10% methanol in methylene chloride. Concentration gave 18.3 mg (72%, 2 steps). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.25-1.32 (m, 6H), 1.40 (m, 4H), 1.54 (m, 5H), 1.65 (m, 4H), 1.83 (m, 2H), 2.30-2.56 (m, 8H), 2.81 (m, 4H), 3.04 (dt, *J*=57.1, 12.2, 1H), 3.43-3.60 (m, 2H), 4.00-4.17 (m, 2H), 4.18-4.26 (m, 3H), 4.49 (m, 1H), 4.62 (m, 1H), 5.03 (m, 1H), 5.80 (dd, *J*=16.8, 9.8, 1H), 6.69 (d, *J*=7.9, 1H), 6.90 (dd, *J*=7.3, 7.3, 1H), 6.99 (dd, *J*=7.6, 7.3, 1H), 7.13 (dd, *J*=7.6, 7.6, 1H), 7.19 (s, 1H), 7.66 (bd, *J*=12.8, 1H). Mass spec.: 646.43 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(6-methoxy-pyridin-3-yl)-acrylic acid methyl ester



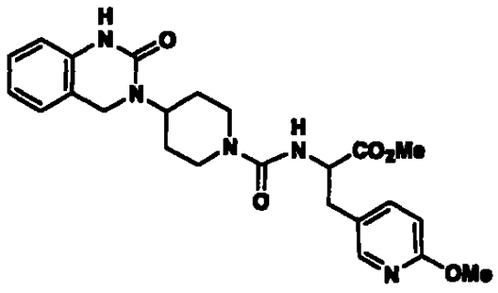
To a suspension of potassium *tert*-butoxide (1.23 g, 1.5 equiv) in methylene chloride (70 mL, -20°C) was added a solution of N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (3.63 g, 1.5 equiv) in methylene chloride (15 mL). The resulting solution was stirred 5 min and treated with the 6-methoxy-pyridine-3-carbaldehyde (1.0 g, 7.3 mmol) in methylene chloride (15 mL). After stirring for 1.5 h, the reaction was warmed to 0°C and stirred 1 h. The reaction was quickly poured into a separatory funnel containing ethyl acetate and water. Brine was added to aid in separation of the layers. The aqueous was extracted with ethyl acetate (3x) which were in turn washed with brine, dried over magnesium sulfate, and concentrated to give 2.63 g (quant.) which was used without purification. Mass spec.: 343.08 $(MH)^+$.

(±)-2-Amino-3-(6-methoxy-pyridin-3-yl)-propionic acid methyl ester



A flask containing 2-benzyloxycarbonylamino-3-(6-methoxy-pyridin-3-yl)-acrylic acid methyl ester (620 mg), palladium on charcoal (10%, 100 mg), ethyl acetate (10 mL) and methanol (20 mL) was flushed with nitrogen, then hydrogen, before finally affixing a balloon of hydrogen. The reaction was allowed to stir overnight. The flask was flushed with nitrogen, filtered through celite, and concentrated to give 390 mg (quant.) which was used without purification. Mass spec.: 211.11 $(MH)^+$.

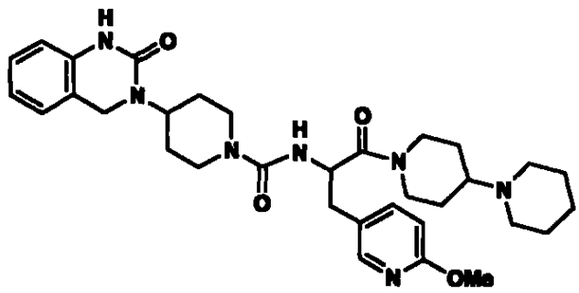
(±)-3-(6-Methoxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



To a solution of 2-amino-3-(6-methoxy-pyridin-3-yl)-propionic acid methyl ester (130 mg) and diisopropylethylamine (0.3 mL) in methylene chloride (2 mL, 0°C) was added *N,N'*-disuccinimidyl carbonate (158 mg). After 30 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (120 mg) in methylene chloride (1 mL) was added via canula. The reaction was warmed to room temperature and stirred overnight. The reaction was concentrated and purified by prep HPLC to give 160mg (55%). Mass spec.: 468.19 $(MH)^+$.

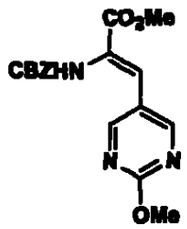
Example 57

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(6-methoxy-pyridin-3-ylmethyl)-2-oxo-ethyl]-amide



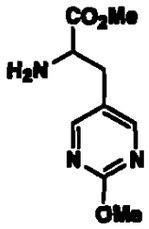
To a solution of 3-(6-methoxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (160 mg) in methanol (6 mL) was added a solution of lithium hydroxide monohydrate (29 mg) in water (1 mL). The reaction was stirred at room temperature for 4 h and cooled to 0°C. The reaction was treated with 1N hydrochloric acid (0.6 mL), concentrated. The residue obtained was dissolved in methylene chloride (5 mL), and treated sequentially with 4-piperidyl-piperidine (75 mg), triethylamine (0.14 mL), and bis-2-oxo-3-oxazolidinyl)phosbinic chloride (104 mg). The reaction was stirred overnight, concentrated, and purified by prep HPLC to give 94 mg (45%). LC/MS: t_R = 1.86 min, 604.51 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(2-methoxy-pyrimidin-5-yl)-acrylic acid methyl ester



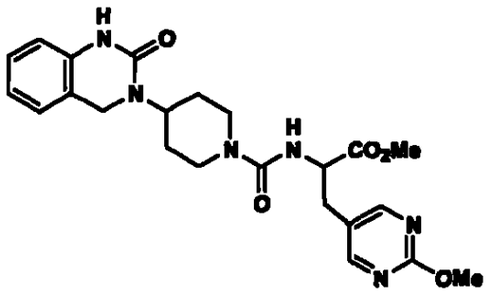
To a suspension of potassium t-butoxide (1.23 g) in methylene chloride (70 mL, -30°C) was added a solution of N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (3.63 g) in methylene chloride (15 mL). The resulting solution was stirred 5 min and treated with the 2-methoxy-pyrimidine-5-carbaldehyde (1.0 g) in methylene chloride (15 mL). After stirring for 1.5 h, the reaction was warmed to 0°C and stirred 1 h. The reaction was quickly poured into a sep funnel containing ethyl acetate and water. Brine was added to aid in separation of the layers. The aqueous was extracted with ethyl acetate (3X) which were in turn washed with brine, dried over magnesium sulfate, and concentrated. The crude product was recrystallized from hot methanol to give 1.4g of pure material. Mass spec.: 344.10 $(MH)^+$.

(±)-2-Amino-3-(2-methoxy-pyrimidin-5-yl)-propionic acid methyl ester



A flask containing amino ester (700 mg), palladium on charcoal (10%, 100 mg) and methanol (20 mL) was flushed with nitrogen, then hydrogen, before finally affixing a balloon of hydrogen. The reaction was allowed to stir overnight. The flask was flushed with nitrogen, filtered through celite, and concentrated to give 379 mg (88%) which was used without purification. Mass spec.: 212.08 $(MH)^+$.

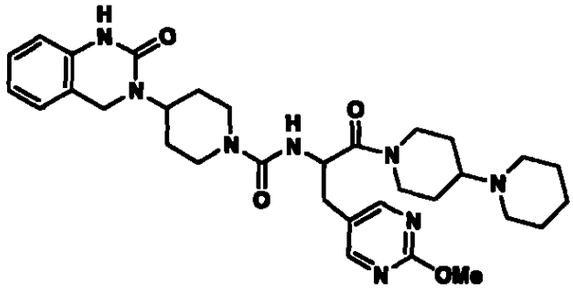
(±)-3-(2-Methoxy-pyrimidin-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



To a solution of 2-Amino-3-(2-methoxy-pyrimidin-5-yl)-propionic acid methyl ester (125 mg) and diisopropylethylamine (0.3 mL) in methylene chloride (2 mL, 0°C) was added *N,N'*-disuccinimidyl carbonate (155 mg). After 30 min, 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (120 mg) in methylene chloride (2 mL) was added via canula. The reaction was warmed to room temperature and stirred overnight. The reaction was concentrated and purified by prep HPLC to give 99mg (36%). Mass spec.: 469.10 $(MH)^+$.

Example 58

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(2-methoxy-pyrimidin-5-ylmethyl)-2-oxo-ethyl]-amide

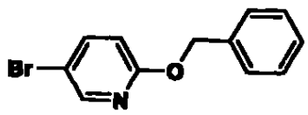


To a solution of 3-(2-methoxy-pyrimidin-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (99 mg) in methanol (6 mL) was added a solution of lithium hydroxide monohydrate (18 mg) in water (1 mL). The reaction was stirred at room temperature for 4 h and cooled to 0°C. The reaction was treated with 1N hydrochloric acid (0.4 mL), concentrated. The residue obtained was dissolved in methylene chloride (3 mL), and treated sequentially with 4-piperidyl-piperidine (50 mg), triethylamine (88 µL), and bis-2-oxo-3-oxazolidinyl)phoshinic chloride (71 mg). The reaction was stirred overnight,

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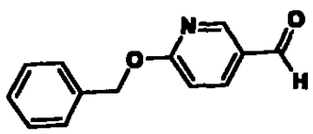
concentrated, and purified by prep HPLC to give 103 mg (45%). LC/MS: t_R = 1.23 min, 605.54 $(MH)^+$.

2-Benzyloxy-5-bromo-pyridine



A suspension of 2,5-dibromopyridine (2.0 g, 8.4 mmol), dibenzo-18-crown-6 (0.14 g, .05 equiv), benzyl alcohol (1.1 mL, 1.3 equiv), and potassium hydroxide (1.1 g, 2.4 equiv) in toluene (30 mL) were heated at reflux for 3 h in an apparatus fitted with a Dean-Stark trap. The suspension was cooled, concentrated, suspended in water, and extracted into methylene chloride. The combined organic phases were washed with water, then brine, dried over magnesium sulfate, and concentrated to give 1.9 g (85%) which was used without purification. Mass spec.: 264.25 $(MH)^+$.

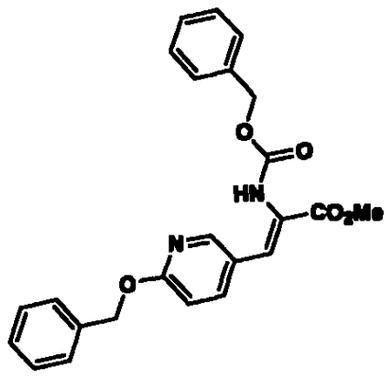
6-Benzyloxy-pyridine-3-carbaldehyde



To a solution of 2-benzyloxy-5-bromo-pyridine (1.64 g, 6.2 mmol) in tetrahydrofuran (25 mL, -78°C) was added n-butyllithium (2.5 M in hexane, 2.61 mL, 1.05 equiv). After 1 h at –78°C, dimethylformamide (0.97 mL, 2 equiv) was added and the mixture stirred for 30 min. The reaction was quickly poured into a stirred solution of 5% aqueous sodium bicarbonate (50 mL) and extracted with diethyl ether (3x). The ethereal was washed with brine, dried over magnesium sulfate, and concentrated to give 1.16 g (quant.) which was used without purification. Mass spec.: 186.34 $(MH)^+$.

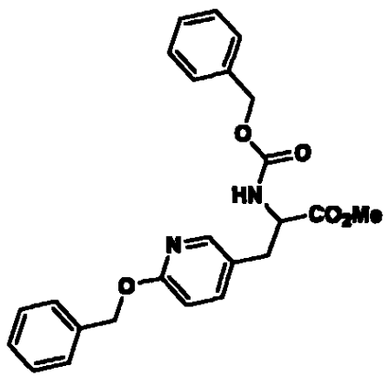
2-Benzyloxycarbonylamino-3-(6-benzyloxy-pyridin-3-yl)-acrylic acid methyl ester

172



To a stirred suspension of potassium *tert*-butoxide (0.440 g, 1.7 equiv) in methylene chloride (25 mL) at -20°C was added N-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (1.3 g, 1.7 equiv) in methylene chloride (5 mL). The resulting solution was stirred for 5 min and treated with the 6-benzyloxy-pyridine-3-carbaldehyde (0.49 g, 2.28 mmol) in methylene chloride (5 mL). The reaction was stirred at –20°C for 1 h, allowed to gradually warm to 0°C, and poured into a separatory funnel containing water and diethyl ether. The reaction was extracted with diethyl ether (2x), washed with brine, dried over magnesium sulfate, and concentrated to give 0.98 g (quant.) as an oil which was used without purification. Mass spec.: 419.32 $(MH)^+$.

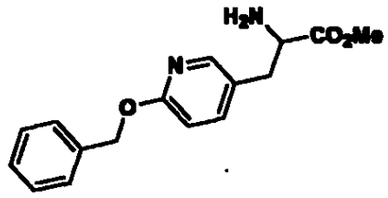
(±)-2-Benzyloxycarbonylamino-3-(6-benzyloxy-pyridin-3-yl)-propionic acid methyl ester



A flask was charged with 2-benzyloxycarbonylamino-3-(6-benzyloxy-pyridin-3-yl)-acrylic acid methyl ester (0.50 g, 1.2 mmol), Wilkinson's catalyst (200 mg, 0.2 equiv), methanol (5 mL), and toluene (3 mL). The flask was flushed with nitrogen, then hydrogen, heated to 35°C, and allowed to stir under an atmosphere of

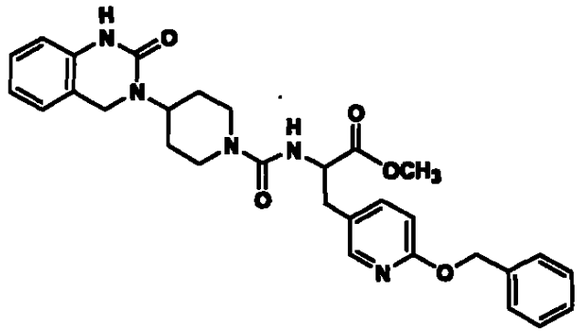
hydrogen for 4 days. The reaction was flushed with nitrogen, diluted with methanol, filtered, and concentrated to afford the crude product which was purified by column chromatography to give 145 mg (29%).

(±)-2-Amino-3-(6-benzyloxy-pyridin-3-yl)-propionic acid methyl ester



To a stirred solution of 2-benzyloxycarbonylamino-3-(6-benzyloxy-pyridin-3-yl)-propionic acid methyl ester (130 mg, 0.31 mmol) in methylene chloride (5 mL, 0°C) was added trimethylsilyl iodide (44 µL, 1.0 equiv). The ice bath was removed and stirring continued for 1 h. Reaction was poured into saturated sodium bicarbonate, extracted with ethyl acetate (3x), washed with brine, dried over magnesium sulfate, and concentrated to give 81mg (91%) which was used without purification. Mass spec.: 287.37 $(MH)^+$.

(±)-3-(6-Benzyloxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester

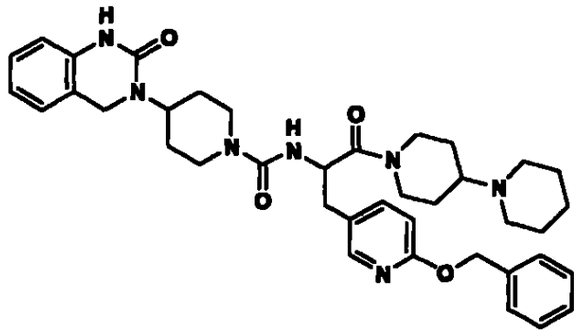


To a stirred solution of 2-amino-3-(6-benzyloxy-pyridin-3-yl)-propionic acid methyl ester (60 mg, 0.21 mmol) in methylene chloride (1 mL, 0°C) was added carbonyl diimidazole (34 mg, 1.0 equiv.). After 15 min, a solution of 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (58 mg, 1.2 equiv.) in methylene chloride (0.5 mL) was added via canula. The ice bath was removed and stirring continued

overnight. The reaction was concentrated and purified by column chromatography to give 59 mg (52%). Mass spec.: 544.49 $(MH)^+$.

Example 59

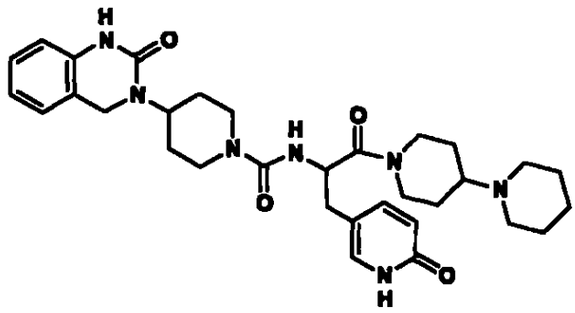
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(6-benzyloxy-pyridin-3-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide



To a stirred solution of 3-(6-benzyloxy-pyridin-3-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (59 mg, 0.11 mmol) in methanol (3 mL) was added a solution of lithium hydroxide monohydrate (9.1 mg, 2 equiv) in water (0.5 mL). The reaction was stirred 2 h at room temperature, cooled to 0°C, quenched by addition of 1N hydrochloric acid (0.15 mL), and concentrated. The crude product was used without purification. The crude acid was dissolved in methylene chloride (2 mL, 0°C), and treated sequentially with 4-piperidino-piperidine (34 mg, 1.8 equiv), triethylamine (35 µL, 2.3 equiv.), and bis-2-oxo-3-oxazolidinyl)phosphinic chloride (34 mg, 1.2 equiv). The ice bath was removed and the reaction allowed to stir overnight. The reaction was concentrated and purified by Prep TLC to give 30.3 mg (41%). LC/MS: t_R = 1.49 min, 680.29 $(MH)^+$.

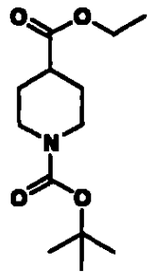
Example 60

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-2-oxo-1-(6-oxo-1,6-dihydro-pyridin-3-ylmethyl)-ethyl]-amide



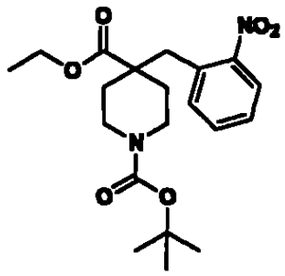
A flask was charged with 4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(6-benzyloxy-pyridin-3-ylmethyl)-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl]-amide (27 mg, 0.04 mmol), palladium on charcoal (10%, 4 mg), and methanol (1 mL). The flask was flushed with nitrogen, then hydrogen, and allowed to stir under an atmosphere of hydrogen overnight. The flask was flushed with nitrogen, and the reaction filtered through celite to give 22.1 mg (94%). LC/MS: $t_R = 0.93$ min, 590.32 $(MH)^+$.

Piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester



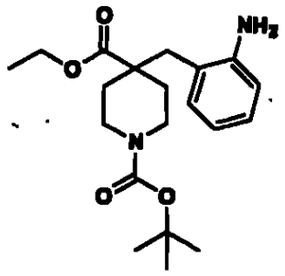
To a solution of ethyl isonipecotate (5.00 g, 0.032 mol) and triethylamine (4.9 mL, 0.035 mmol) in dichloromethane (25 mL) at 0°C was slowly added a solution of di-*tert*-butyldicarbonate (7.2 g, 0.033 mol) in dichloromethane (25 mL). The reaction mixture was stirred at room temperature overnight, then washed with potassium hydrogen sulfate three times and with brine once. The organic extract was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give the desired product (8.23 g, 100%) as colorless oil. ^1H NMR (C_6D_6, 500 MHz) δ 3.88 (q, $J = 7.5$ Hz, 2H), 2.52 (m, 1H), 1.60-1.48 (m, 8H), 1.42 (s, 9H), 0.92 (t, 3H). Mass spec.: 280.44 $(M+Na)^+$.

4-(2-Nitro-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester



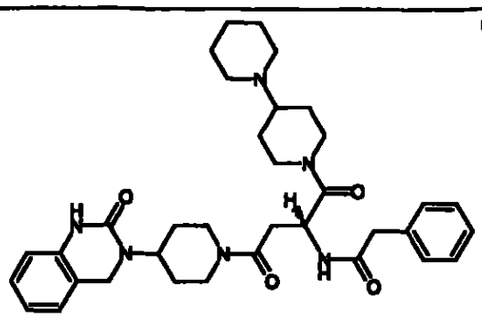
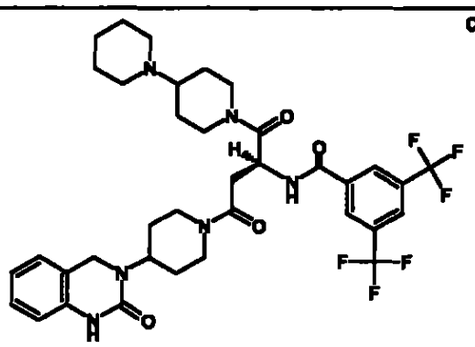
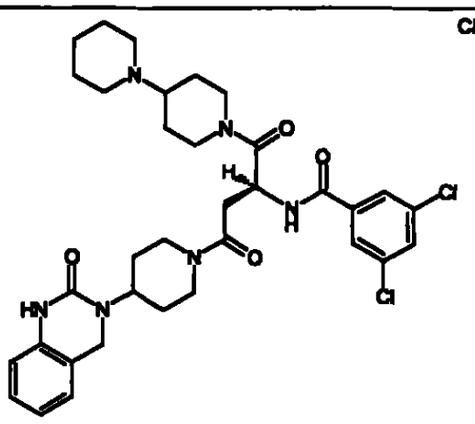
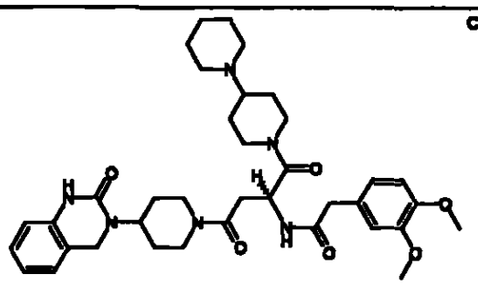
To a solution of piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (8.23 g, 0.032 mol) in tetrahydrofuran (85 mL) was slowly added a solution of sodium bis(trimethylsilyl)amide (44 mL, 0.044 mol). After the resulting mixture had been stirred at –78°C for 1 h, a solution of 2-nitrobenzyl bromide (8.21 g, 0.038 mol) was added. The reaction mixture was allowed to warm up to room temperature and was stirred overnight. It was then concentrated and the residue was partitioned between water and ethyl acetate. The organic extract was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under vacuum. The final product was purified from the complex reaction mixture by way of column chromatography on silica gel (eluent – hexanes – ethyl acetate 4:1) to give the desired product (1.61 g, 13%) as brown oil. Mass spec.: 415.38 $(M+Na)^+$.

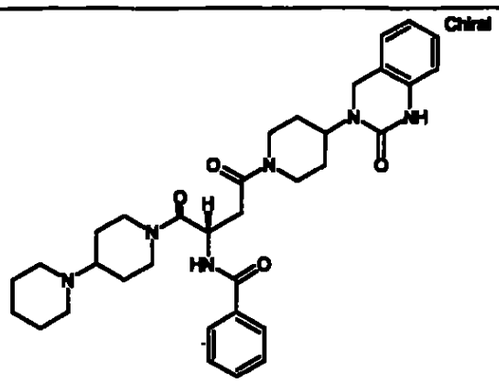
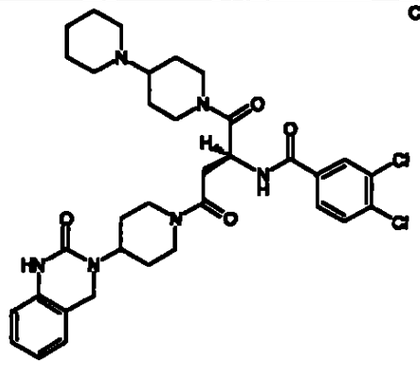
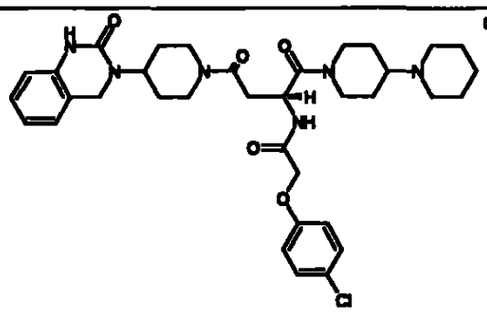
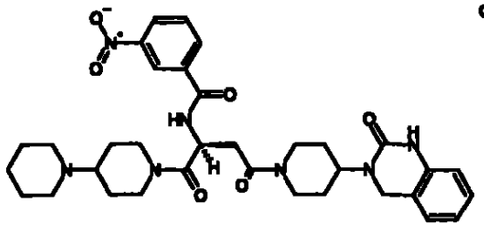
4-(2-Amino-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester



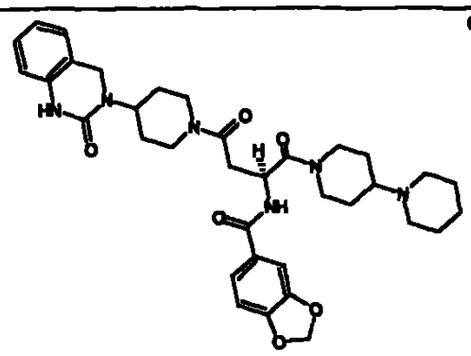
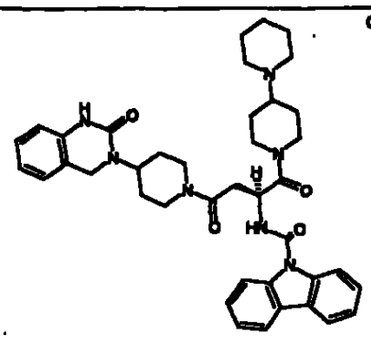
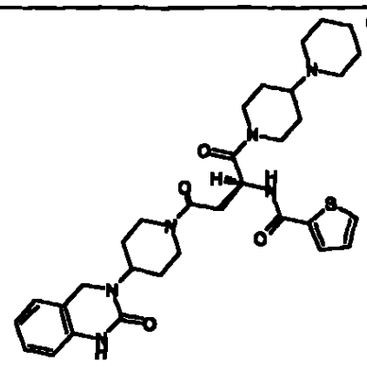
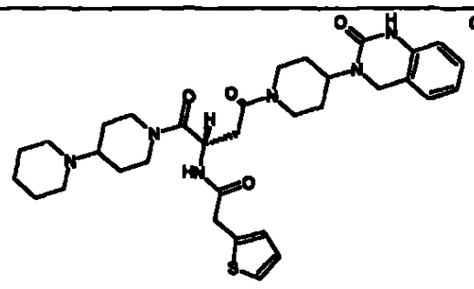
A mixture of 4-(2-nitro-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.61 g, 4.102 mmol) and 10% palladium on charcoal (0.10 g) in ethanol (190 mL) was hydrogenated at 50 psi overnight. The resultant mixture was filtered through a plug of celite, and the filtrate concentrated under vacuum to provide the desired product (1.29 g, 99%) as colorless oil. Mass spec.: 363.45 $(MH)^+$.

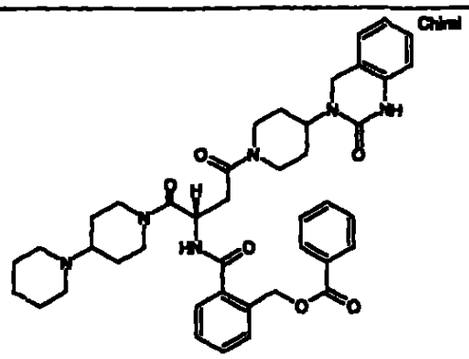
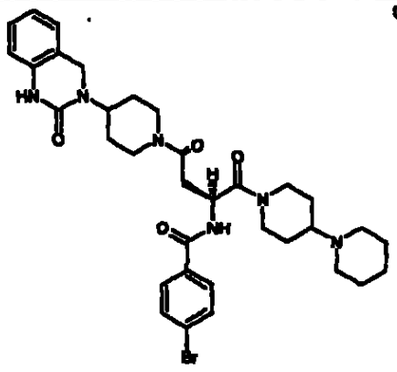
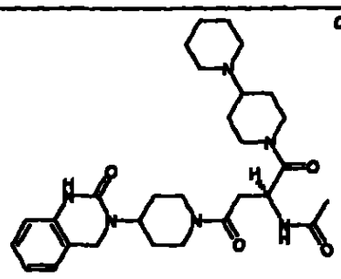
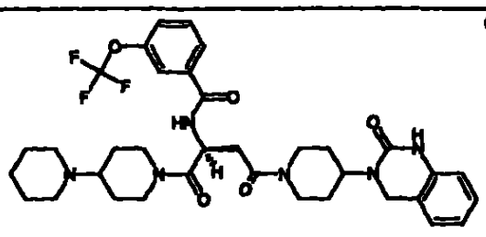
4-(2-Amino-benzyl)-piperidine-4-carboxylic acid ethyl ester hydrochloride

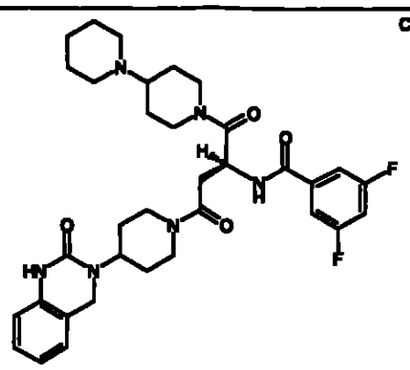
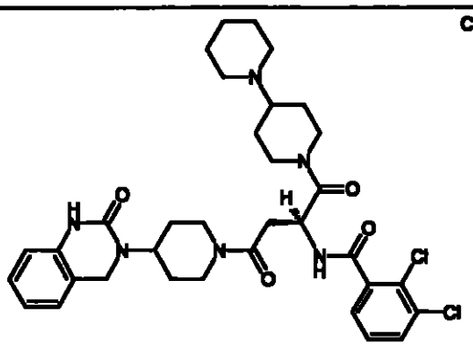
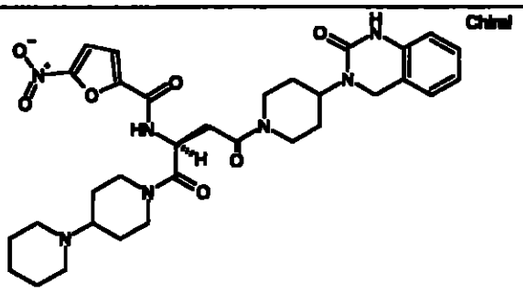
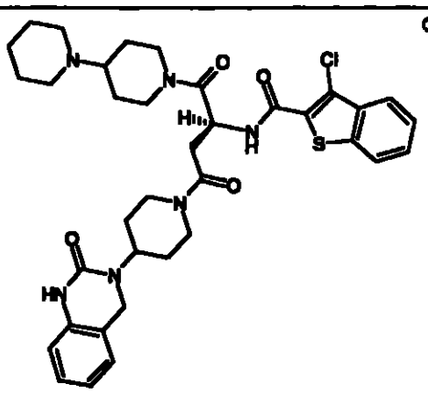
Example	Structure	HPLC t_R (min)	MS (M+)
106	 Chiral	1.62	615.41
107	 Chiral	2.25	737.37
108	 Chiral	2.12	669.3
109	 Chiral	1.59	675.46

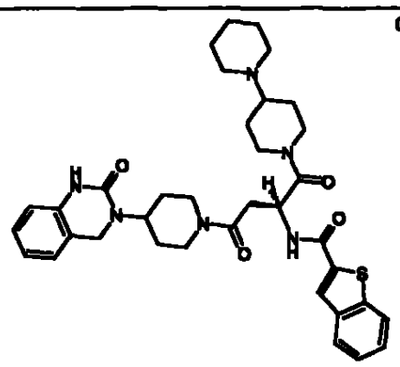
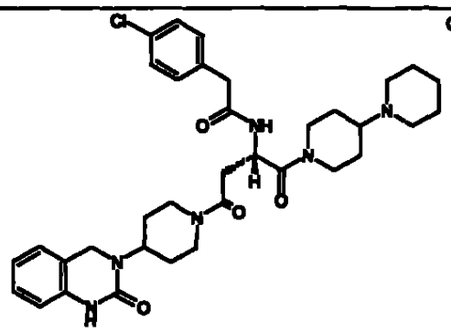
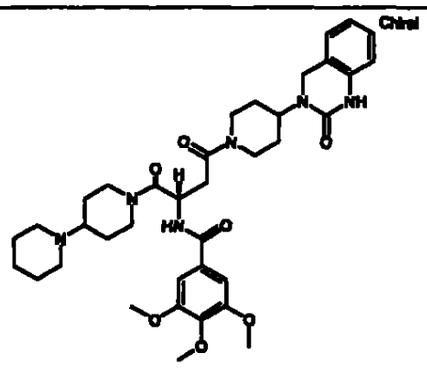
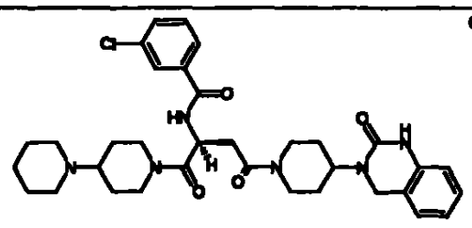
Example	Structure	HPLC t_R (min)	MS (M+)
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111		2.09	669.33
112		1.91	665.36
113		1.68	646.37

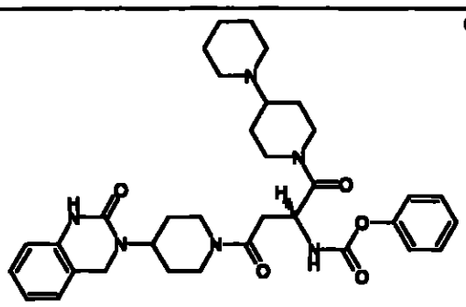
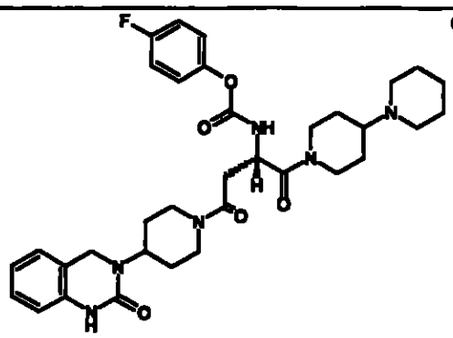
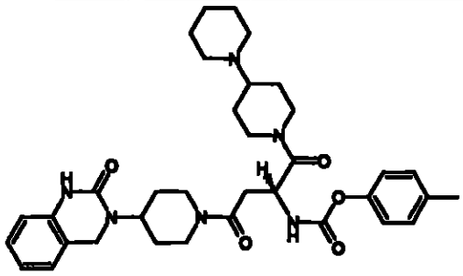
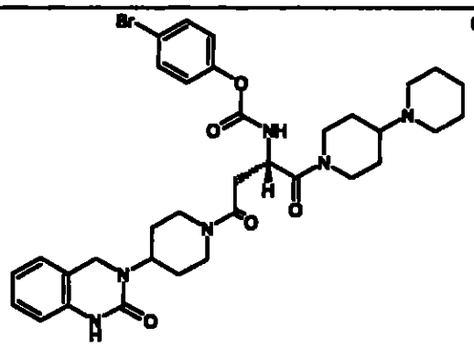
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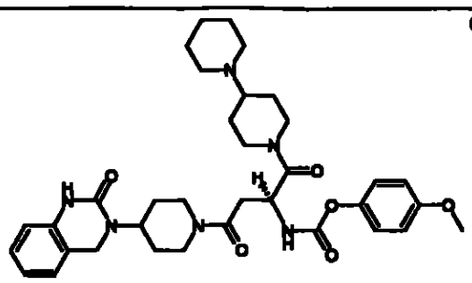
Example	Structure	HPLC t_R (min)	MS (M+)
114		1.66	645.4
115		2.14	690.45
116		1.59	607.39
117		1.59	621.4

Example	Structure	HPLC t_R (min)	MS (M+)
118		2.01	735.43
119		1.92	679.32
120		1.22	537.4
121		2.03	685.4

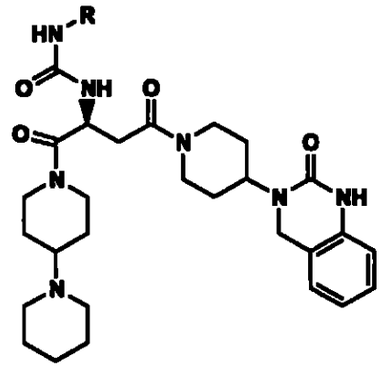
Example	Structure	HPLC t_R (min)	MS (M+)
122		1.79	637.38
123		1.84	669.3
124		1.53	636.35
125		2.04	691.35

Example	Structure	HPLC t_R (min)	MS (M+)
126		1.89	657.35
127		1.86	649.39
128		1.67	691.42
129		1.84	635.38

Example	Structure	HPLC t_R (min)	MS (M+)
130		1.69	617.42
131		1.74	635.38
132		1.84	631.44
133		1.94	695.28

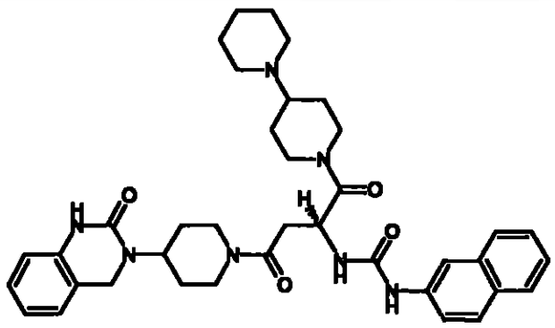
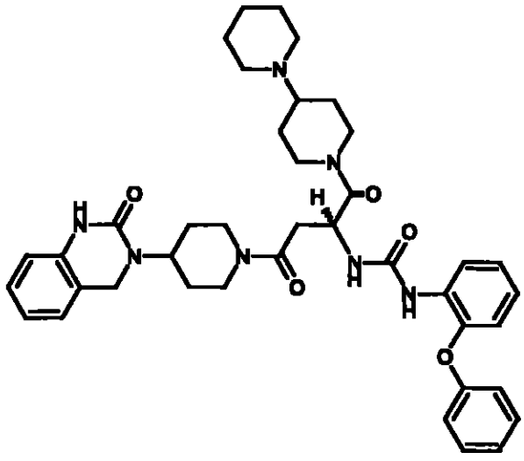
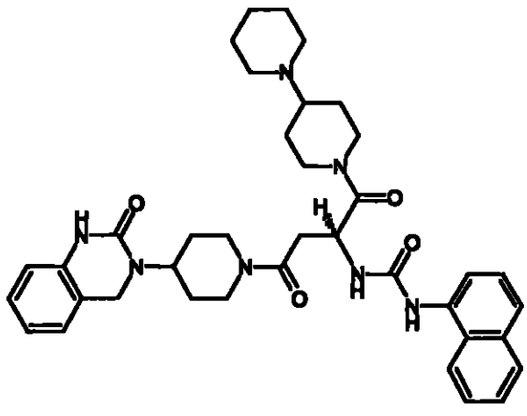
Example	Structure	HPLC t_R (min)	MS (M+)
134		1.7	647.41

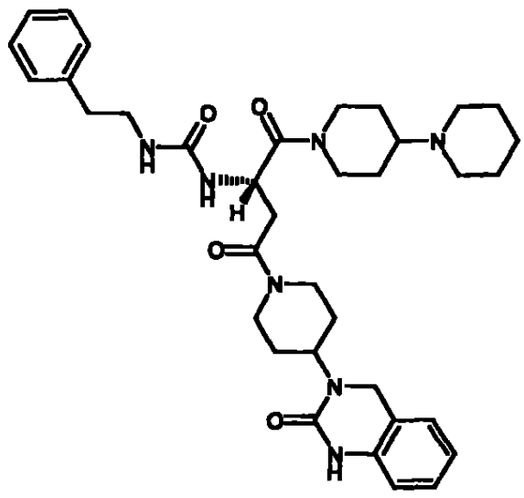
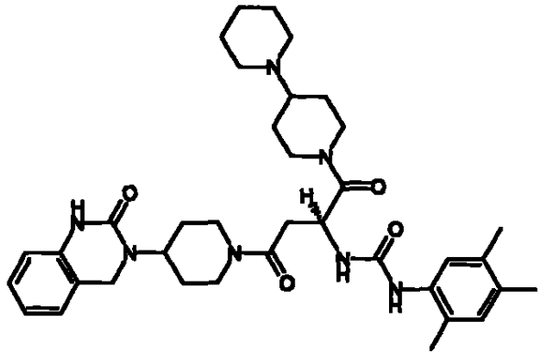
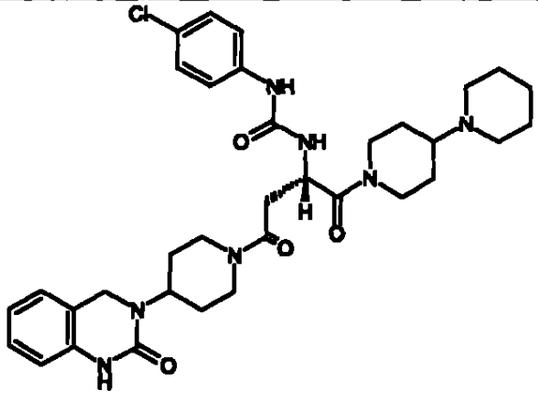
General procedure for the synthesis of Examples 135-200:

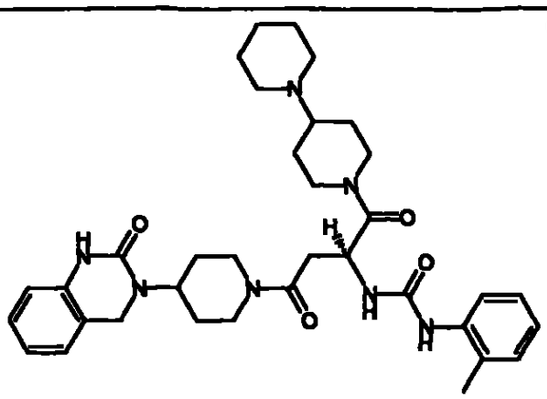
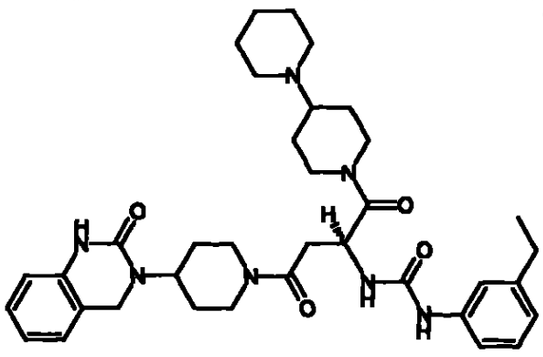
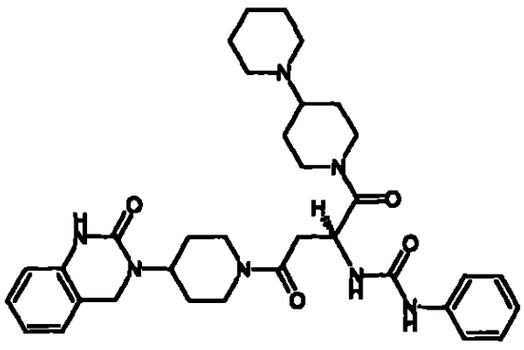


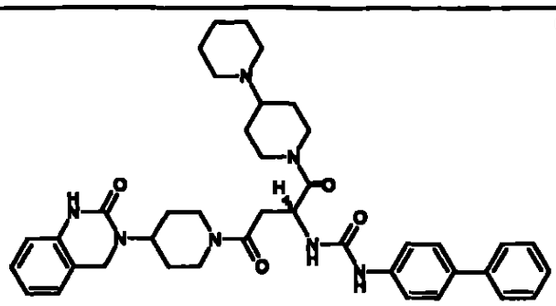
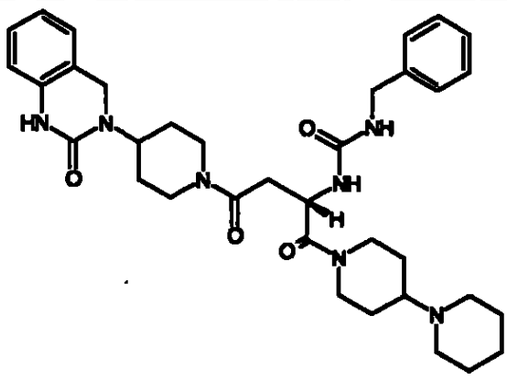
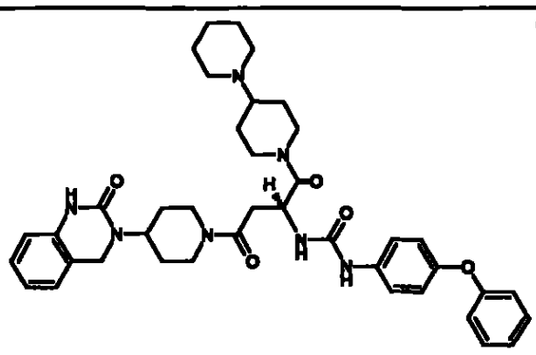
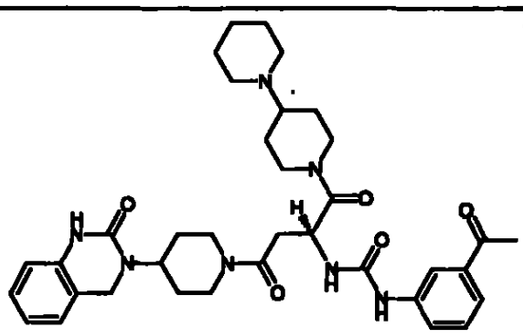
The starting amine, 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione, was dispersed in a 96-well mini-reactor (ca. 10 mg in each well) in dichloroethane (1 mL). Individual isocyanates (ca. 2 equiv) were added to individual wells. The block was shaken for 2 days. Approximately 4 equivalent of tris-amine resin was added to each well and the mini-reactor was shaken for another two days. The reaction mixtures were filtered, and individual product was purified by either preparative HPLC or filtration through an SCX cartridge or both. HPLC retention times and mass spectral data for each example are listed in Table 3.

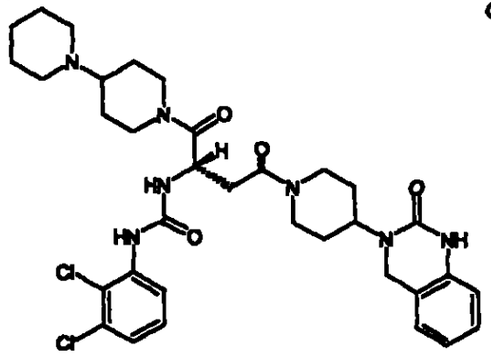
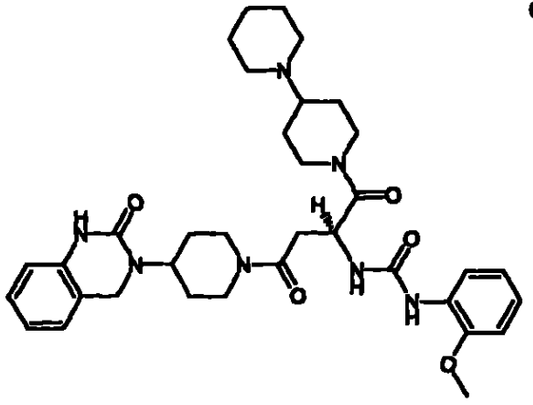
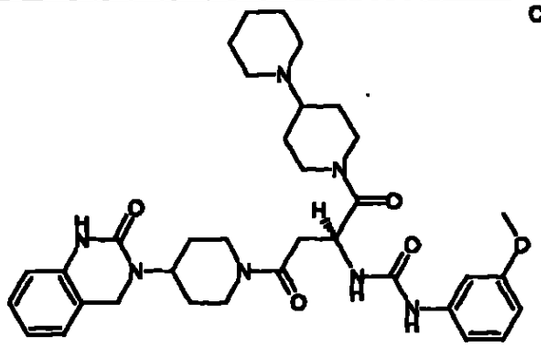
Table 3. Ureas

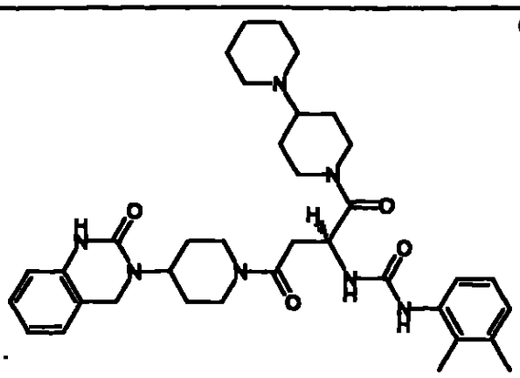
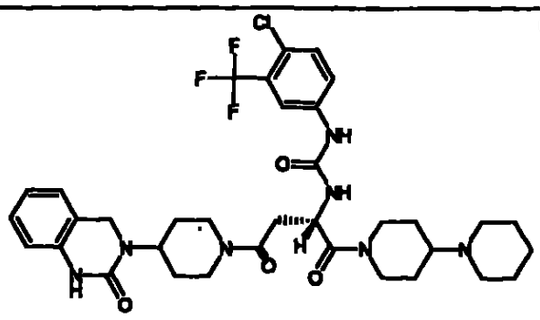
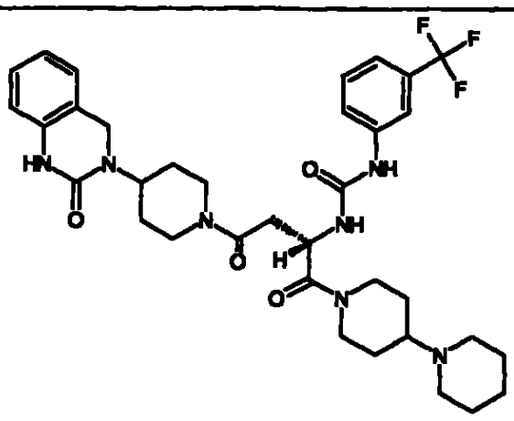
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
135	Chiral 	1.43	665.84
136	Chiral 	1.56	707.88
137	Chiral 	1.39	665.84

Example	Structure	HPL C t_R (min)	MS $(MH)^+$
138	 Chiral	1.3	643.83
139	 Chiral	1.44	657.86
140	 Chiral	1.42	650.22

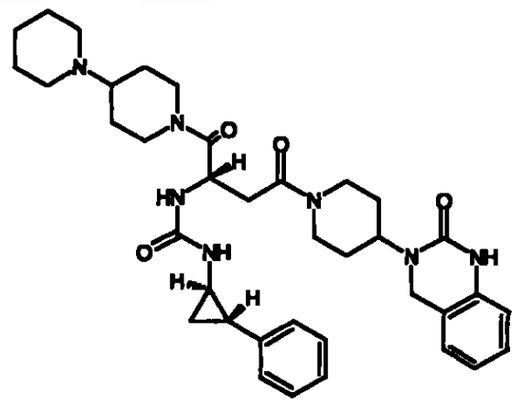
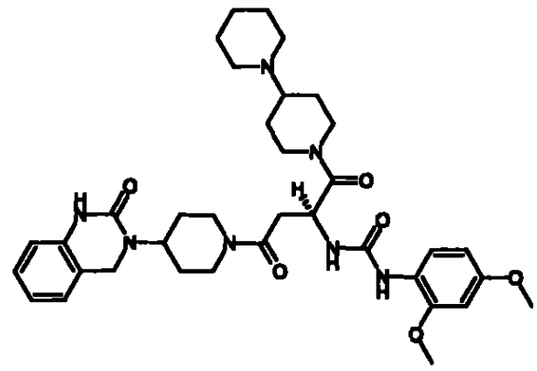
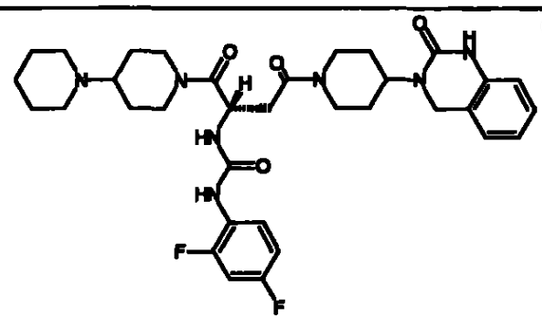
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
141	Chiral 	1.26	629.81
142	Chiral 	1.41	643.83
143	Chiral 	1.24	615.78

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
144	Chiral 	1.53	691.88
145	Chiral 	1.21	629.81
146	Chiral 	1.52	707.88
147	Chiral 	1.19	657.82

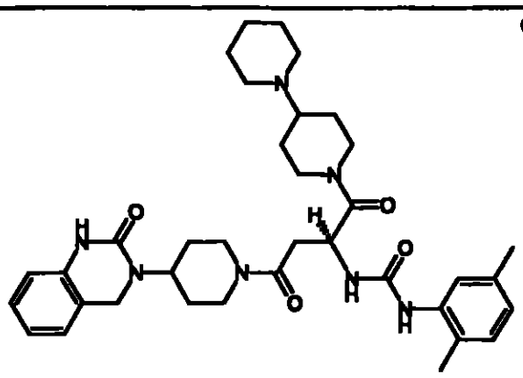
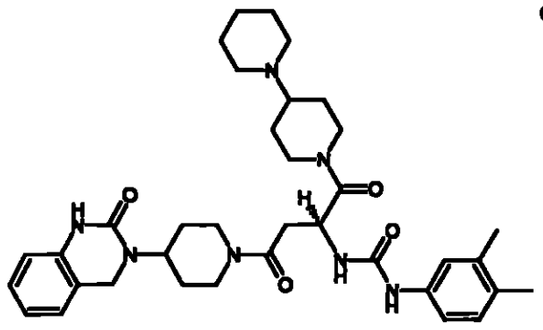
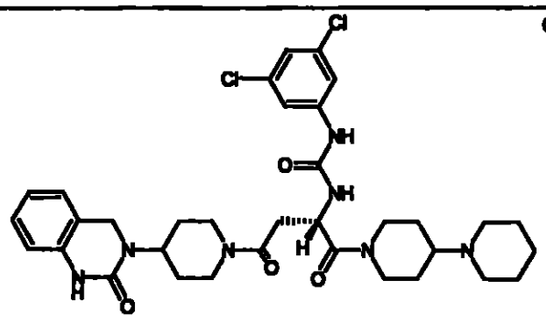
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
148	Chiral 	1.44	684.67
149	Chiral 	1.3	645.81
150	Chiral 	1.24	645.81

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
151	Chiral 	1.33	643.83
152	Chiral 	1.56	718.22
153	Chiral 	1.55	683.78

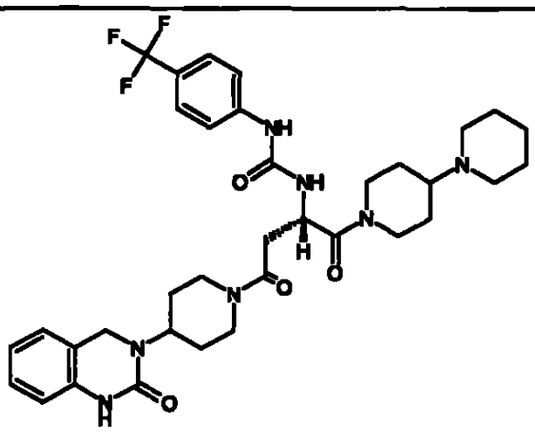
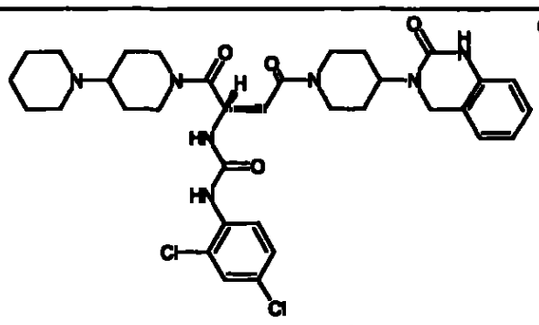
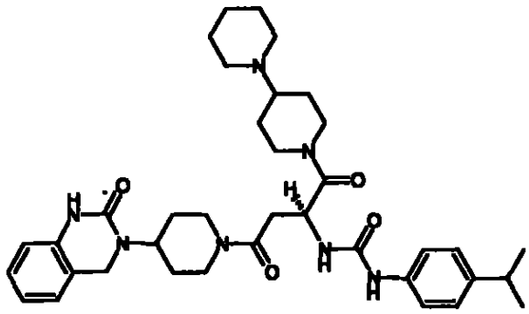
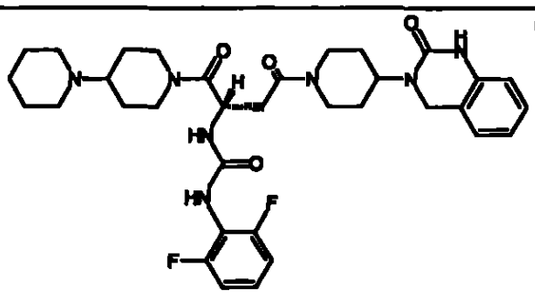
191

Example	Structure	HPL C t_R (min)	MS $(MH)^+$
154	 Chiral	1.37	655.84
155	 Chiral	1.27	675.83
156	 Chiral	1.26	651.76

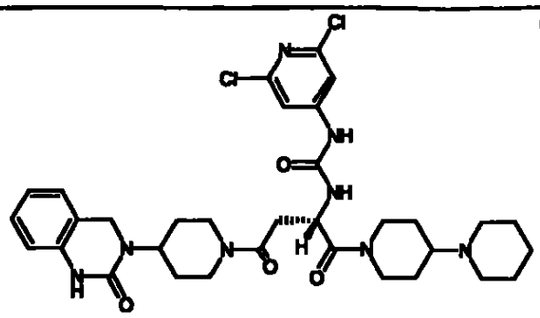
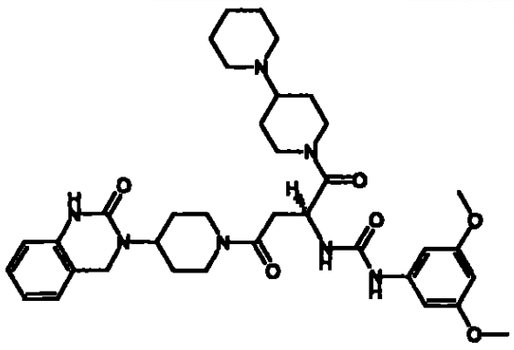
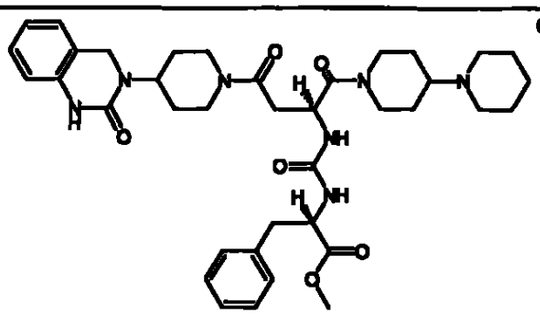
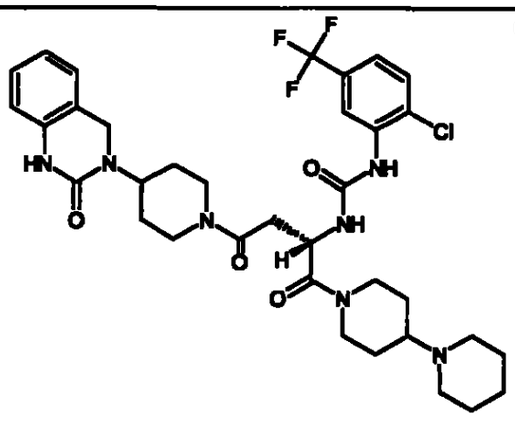
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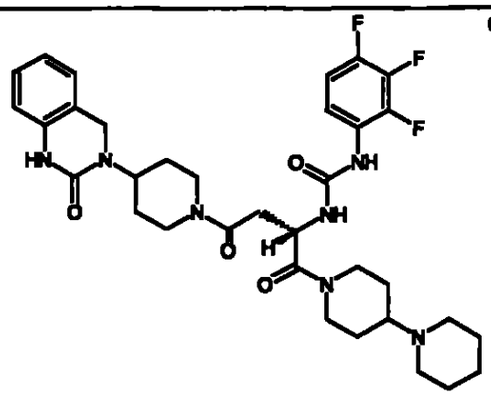
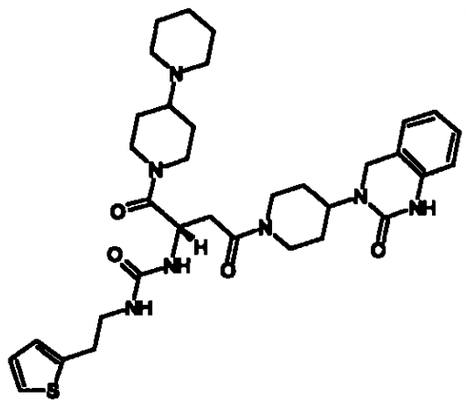
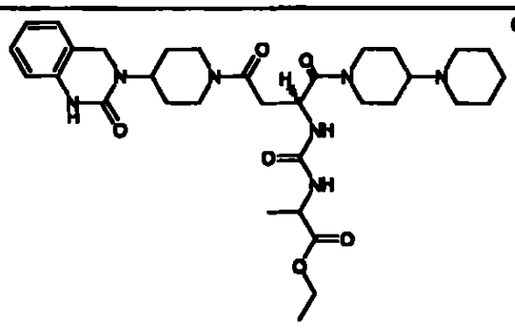
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
157	Chiral 	1.39	643.83
158	Chiral 	1.43	643.83
159	Chiral 	1.57	684.67

193

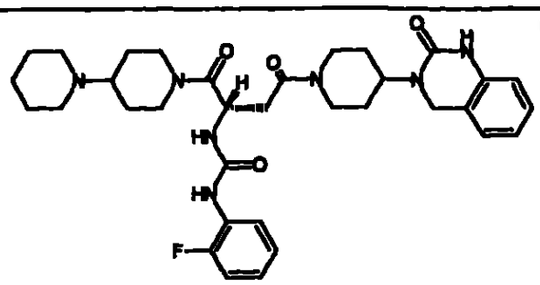
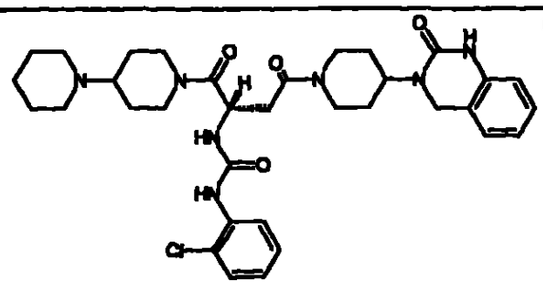
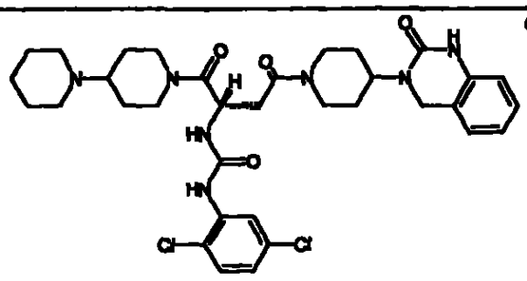
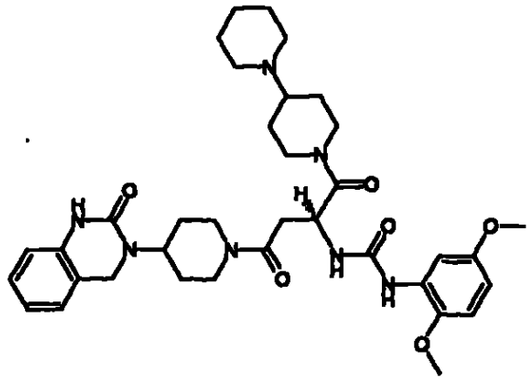
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
160	 Chiral	1.46	683.78
161	 Chiral	1.48	684.67
162	 Chiral	1.5	657.86
163	 Chiral	1.14	651.76

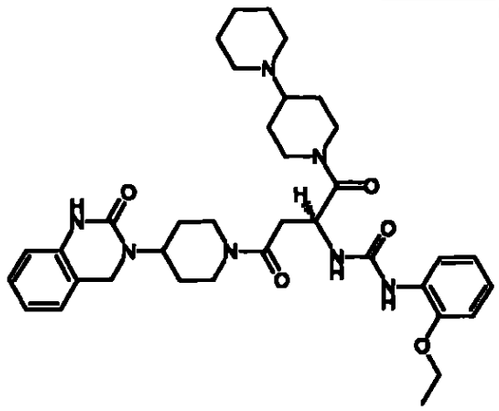
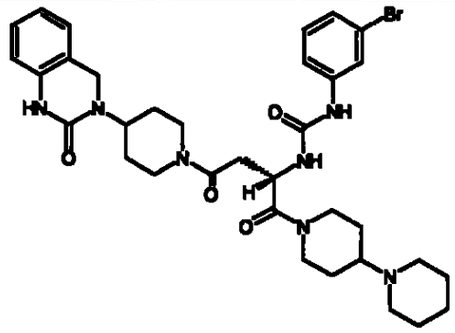
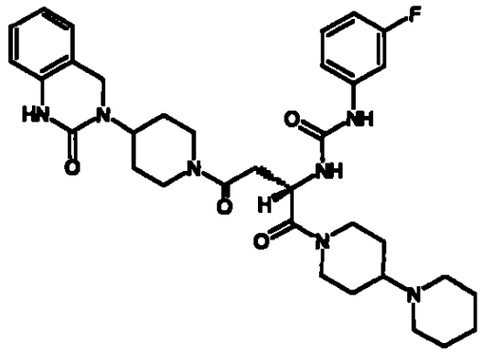
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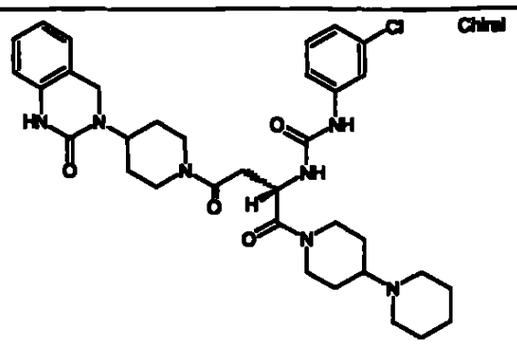
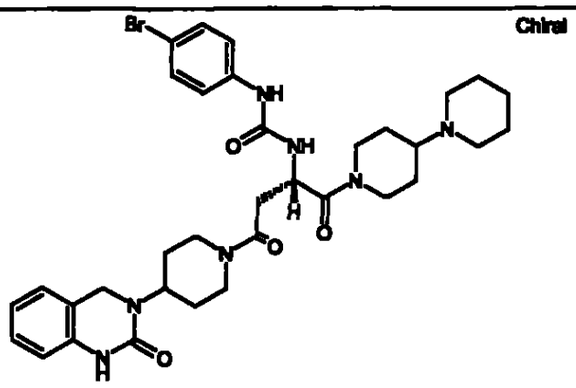
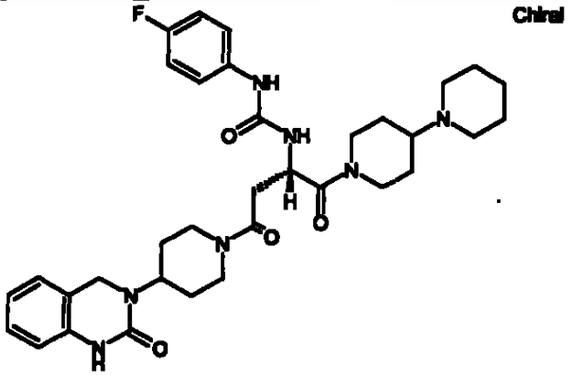
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
164	 Chiral	1.34	685.66
165	 Chiral	1.26	675.83
166	 Chiral	1.28	701.87
167	 Chiral	1.52	718.22

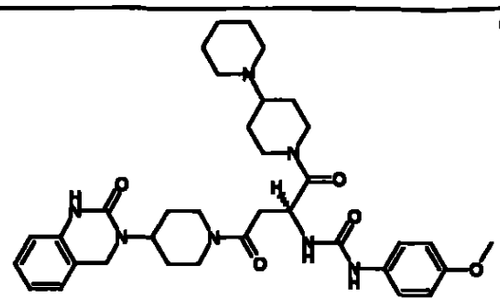
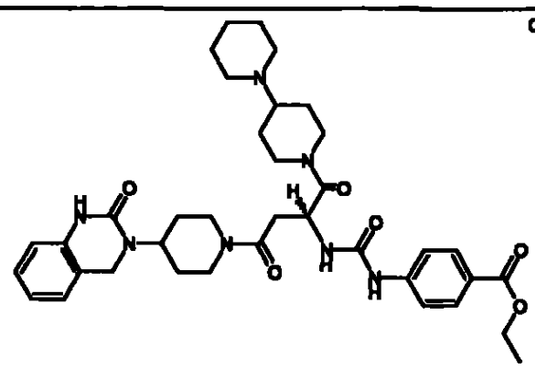
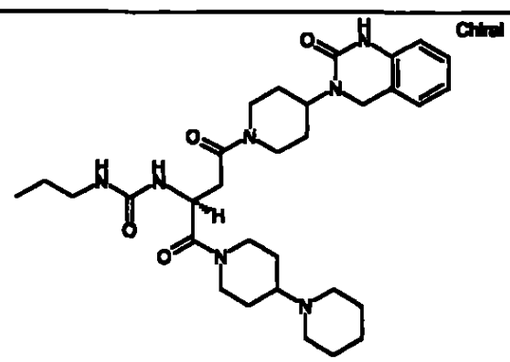
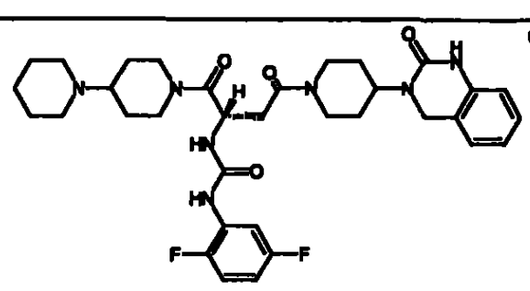
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
168	 Chiral	1.35	669.75
169	 Chiral	1.24	649.86
170	 Chiral	1.11	639.8

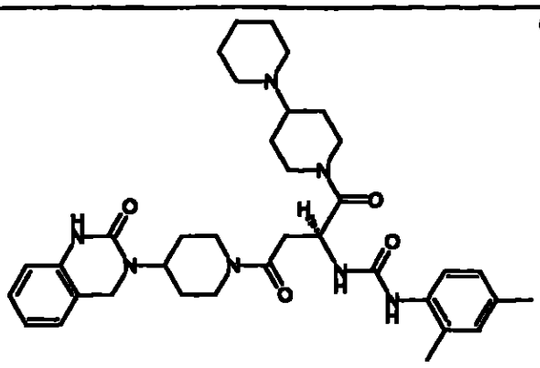
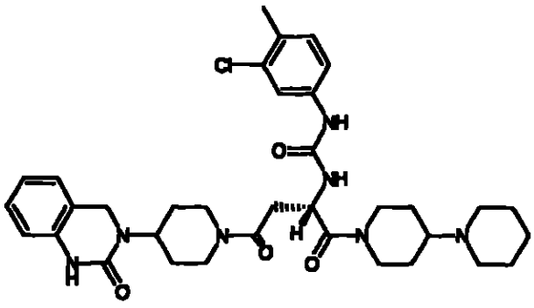
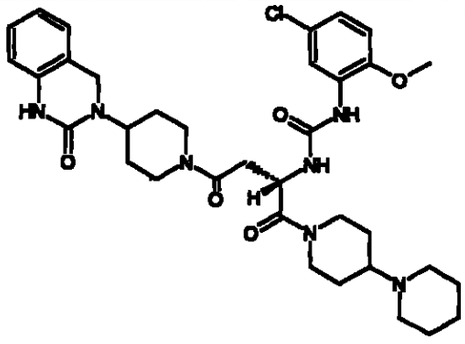
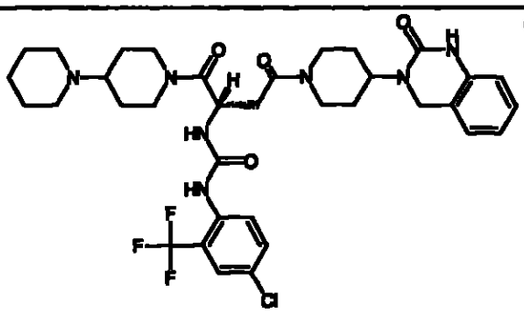
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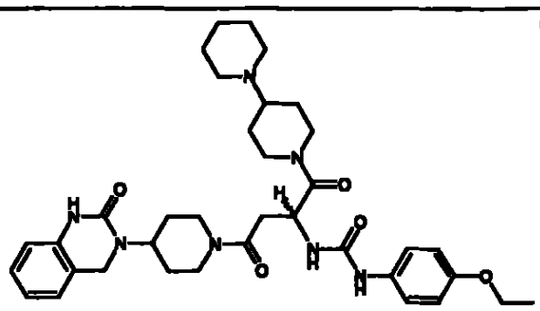
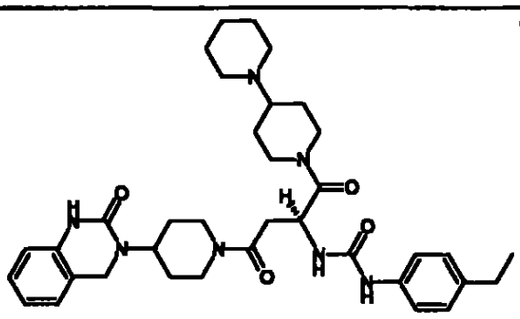
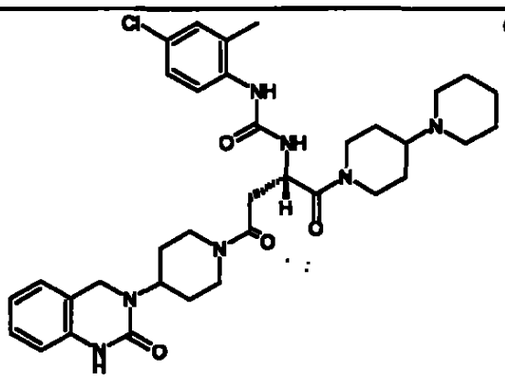
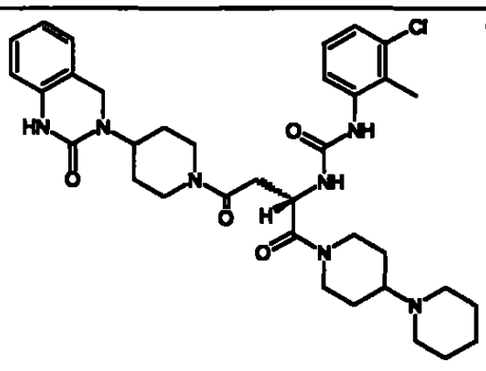
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
171	 Chiral	1.31	633.77
172	 Chiral	1.34	650.22
173	 Chiral	1.47	684.67
174	 Chiral	1.27	675.83

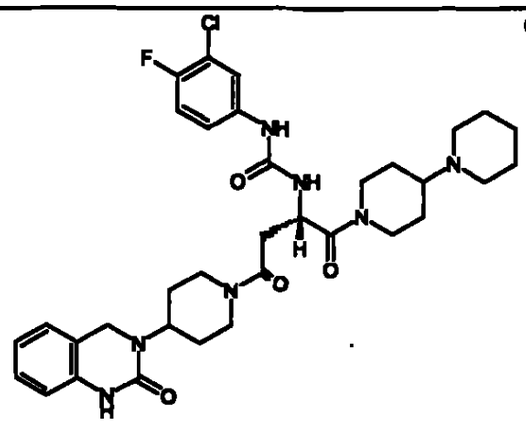
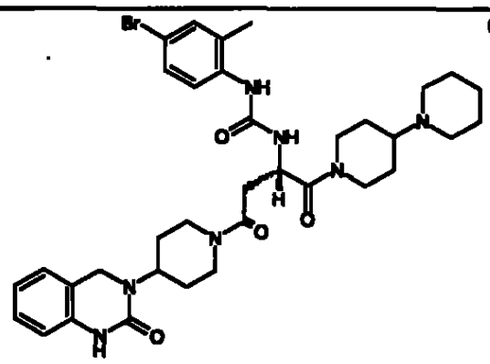
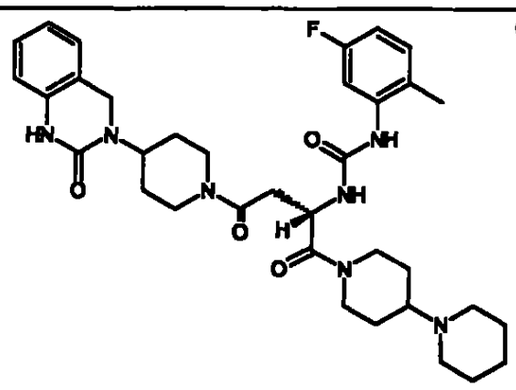
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
175	 Chiral	1.34	659.83
176	 Chiral	1.41	694.68
177	 Chiral	1.28	633.77

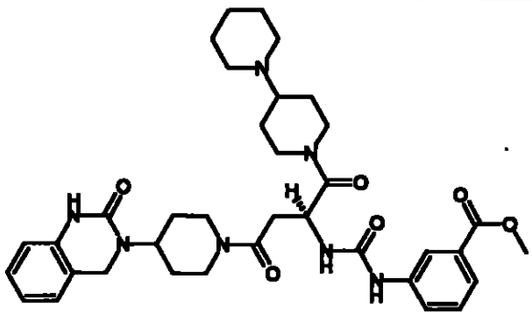
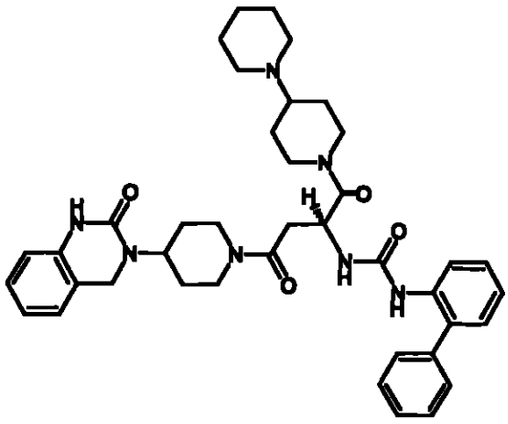
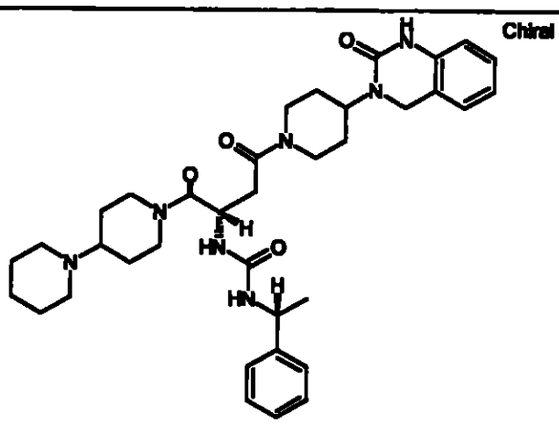
Example	Structure	HPL C t_R (min)	MS $(MH)^+$
178		1.39	650.22
179		1.42	694.68
180		1.26	633.77

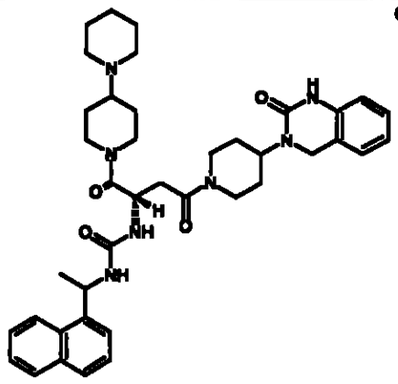
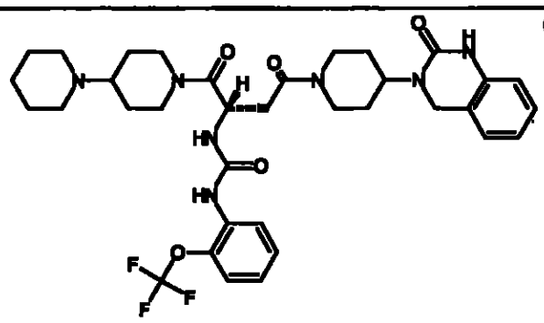
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
181		1.19	645.81
182		1.34	687.84
183		1.08	581.76
184		1.31	651.76

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
185	 Chiral	1.39	643.83
186	 Chiral	1.33	664.25
187	 Chiral	1.41	680.25
188	 Chiral	1.48	718.22

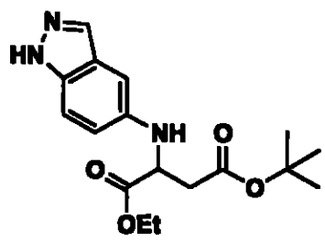
Example	Structure	HPLC t_R (min)	MS $(MH)^+$
189	 Chiral	1.28	659.83
190	 Chiral	1.41	643.83
191	 Chiral	1.41	664.25
192	 Chiral	1.41	664.25

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
193	 Chiral	1.41	668.21
194	 Chiral	1.45	708.71
195	 Chiral	1.39	647.8

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
196	Chiral 	1.27	673.82
197	Chiral 	1.45	691.88
198	Chiral 	1.26	643.83

Example	Structure	HPLC t_R (min)	MS $(MH)^+$
199		1.45	693.89
200		1.4	699.78

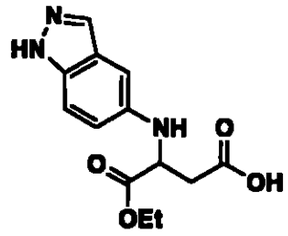
2-(1H-Indazol-5-ylamino)-succinic acid 4-*tert*-butyl ester 1-ethyl ester



To a solution/suspension of 5-aminoindazole (1.01 g, 7.6 mmol) in tetrahydrofuran (20 mL) was added ethyl glyoxlate solution (ca. 50% in toluene, 1.7 mL, 1.1 equiv) in one portion followed by magnesium sulfate (4.6 g). The mixture was stirred at room temperature overnight (23 h) and then filtered and concentrated *in vacuo*. The resulting crude imine intermediate (1.3 g, 6 mmol) was dried by azeotroping with anhydrous benzene and further dried under high vacuum. The residue was then dissolved in tetrahydrofuran (20 mL) and cooled at 0°C. A solution of 2-*tert*-butoxy-2-oxoethylzinc chloride (0.5 M in ether, 24 mL, 2 equiv) was then

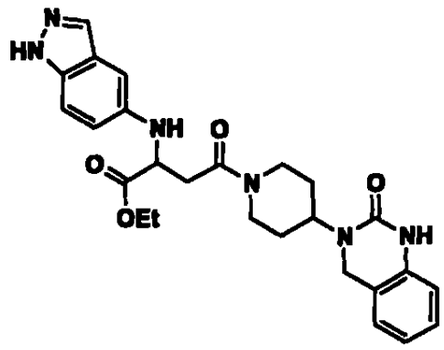
slowly added. After stirring at 0°C for 1 h, the mixture was stored at 4°C overnight. The mixture was then diluted with ethyl acetate and quenched with half-saturated ammonium chloride solution along with a minimum amount of 0.5 N HCl to dissolve the precipitated solids. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel, eluting with 10% methanol in methylene chloride, to afford the desired product (1.3 g, 65%) as a tan oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, s), 7.40 – 7.27 (1H, m), 6.98 – 6.77 (2H, m), 4.42 – 4.35 (1H, m), 4.30 – 4.12 (3H, m), 2.80 (2H, d, J = 4.4 Hz), 1.43 (9H, s), 1.27 – 1.17 (4H, m). Mass spec.: 356.24 $(M+Na)^+$, 278.23 $(M - {}^tBu)^+$, t_R = 1.287 min.

2-(1H-Indazol-5-ylamino)-succinic acid 1-ethyl ester



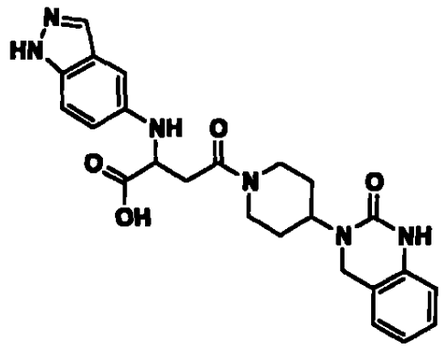
A stirred solution of 2-(1H-indazol-5-ylamino)-succinic acid 4-*tert*-butyl ester 1-ethyl ester (123.6 mg, 0.37 mmol) in methylene chloride (2 mL) and trifluoroacetic acid (0.5 mL) was stirred at room temperature overnight. The reaction mixture was then diluted with ethyl acetate and washed with saturated ammonium chloride solution, water and brine. The organic layer was dried and concentrated to give a dark green oil: LC/MS: t_R = 0.643 min, 278.19 $(MH)^+$.

2-(1H-Indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid ethyl ester



To a stirred solution of 2-(1H-indazol-5-ylamino)-succinic acid 1-ethyl ester (84 mg, 0.215 mmol) in methylene chloride (1mL) was added the amine (99 mg, 0.429 mmol, 2 equiv) followed by DEPBT (128 mg, 0.43 mmol, 2 equiv.) and triethylamine (70 µL, 0.47 mmol, 2.2 equiv). The mixture was stirred overnight and then diluted with ethyl acetate and washed with half-saturated ammonium chloride solution, water and brine. The organic layer was dried and concentrated to a tan oil. The crude product was purified by flash column chromatography on silica gel, eluting with 10% methanol in methylene chloride, to give the desired product (36.2 mg, 34.5% for two steps) as a reddish oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 4.4 Hz), 7.33 (1H, d, J = 8.4 Hz), 7.20 – 7.14 (1H, m), 7.00 – 6.80 (4H, m), 6.70 (1H, t, J = 6.8 Hz), 4.58 – 4.48 (1H, m), 4.65 – 4.40 (2H, m), 4.34 – 4.05 (3H, m), 4.02 – 3.82 (1H, m), 3.20 – 2.99 (2H, m), 2.99 – 2.84 (1H, m), 2.70 – 2.52 (1H, m),1.80 – 1.50 (5H, m), 1.35 – 1.12 (5H, m). LC/MS: t_R = 1.130 min, 491.37 $(MH)^+$.

2-(1H-Indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid

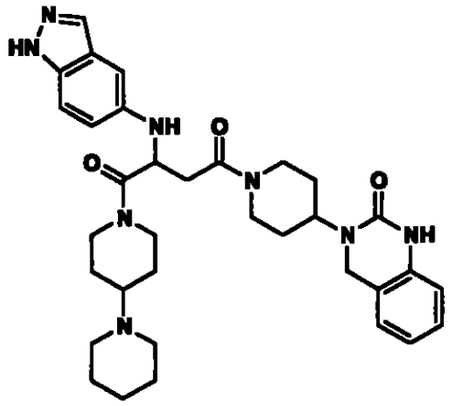


To a solution of the ethyl ester (34 mg, 0.069 mmol) in tetrahydrofuran (0.3 mL) was added lithium hydroxide in water(1M, 280 µL, 4 equiv) and the mixture

was stirred at room temperature for 17 h. The solution was dried under a stream of nitrogen. To the residue was added 0.2 mL tettrahydrofuran and 0.2 mL anhydrous benzene and the suspension was blown dry again with a stream of nitrogen. LC/MS: t_R = 0.900 min, 463.30 $(MH)^+$.

Example 201

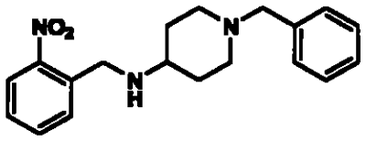
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indazol-5-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



To a solution of 2-(1H-indazol-5-ylamino)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid ethyl ester (0.069 mmol) in dimethylformamide (0.5 mL) in a capped drum vial was added piperidinylpiperidine (14.3 mg, 0.076 mmol, 1.1 equiv), DEPBT (22.8 mg, 1.1 equiv) and triethylamine (8 drops, ca. 160 µL). The mixture was stirred at room temperature overnight. The final product was purified by preparative HPLC to afford the desired product (15 mg, 26% for two steps) as a tan solid. LC/MS: t_R = 0.917 min, 613.54 $(MH)^+$.

Additional Examples

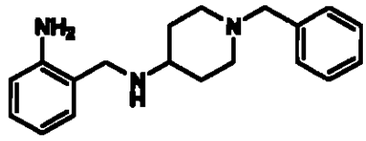
(1-Benzyl-piperidin-4-yl)-(2-nitro-benzyl)-amine



2-Nitrobenzaldehyde (1 g, 6.61 mmol) and 4-amino-1-benzylpiperidine (1.35 mL, 6.61 mmol) were combined in ethanol (20 mL). The resulting suspension was

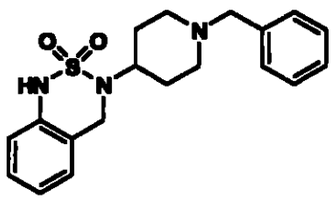
stirred at room temperature for 20 min before a solution of sodium borohydride (0.25 g, 6.61 mmol) in ethanol (5 mL) was added dropwise over 10 min. After the addition was complete, the reaction was stirred for 1 h, cooled to 0°C and concentrated ammonium chloride was added to the reaction mixture until no bubbling was observed. The solvents were evaporated *in vacuo* and the resultant crude mixture was dissolved in water (10 mL) and methylene chloride (10 mL). The layers were separated and the organic layer washed with water (2x) and brine (2x), dried over sodium sulfate, filtered, and concentrated to afford 1.5 g (70%) of the desired product. LC/MS: t_R = 0.7 min, 326.18 $(MH)^+$.

(2-Amino-benzyl)-(1-benzyl-piperidin-4-yl)-amine



(1-Benzyl-piperidin-4-yl)-(2-nitro-benzyl)-amine (1.2 g, 3.7 mmol) and zinc dust (1 g, excess) were combined in 75% aqueous acetic acid (16 mL) and stirred at 60°C for 2 h. After cooling to room temperature, the solvents were removed *in vacuo* and the resultant crude dissolved in water (10 mL), followed by addition of ammonium hydroxide until pH 3 was attained. The solution was extracted with methylene chloride (3x). The organic layers were pooled together washed with water (2x), brine (2x), dried over sodium sulfate, filtered, and concentrated to afford 0.8 g (73%) of the desired product. ^{1}H-NMR (CD_3OD) δ 2.50 (m, 2H), 3.20 (m, 2H), 3.49 (dd, *J*=7.0, 7.3, 1H), 3.62 (m, 4H), 4.20 (s, 2H), 4.36 (s, 2H), 7.04 (m, 2H), 7.32 (dd, *J*=7.3, 7.6, 1H), 7.41 (d, J=7.9, 1H), 7.50 (m, 5H). Mass spec.: 296.40 $(MH)^+$.

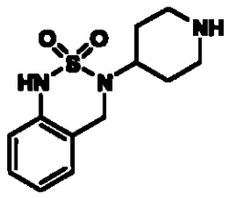
3-(1-Benzyl-piperidin-4-yl)-3,4-dihydro-1H-benzo[1,2,6]thiadiazine-2,2-dioxide



A solution of (2-amino-benzyl)-(1-benzyl-piperidin-4-yl)-amine (1.0 g, 3.39 mmol) and sulfamide (0.64 g, 6.78 mmol) in pyridine was heated at reflux for 14 h.

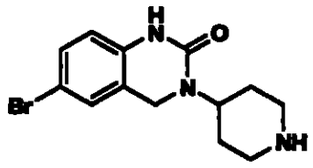
After cooling to room temperature, the solvent was evaporated and the crude product dissolved in water. After being adjusted to pH 9 with 6N sodium hydroxide, the resulting mixture was extracted with methylene chloride (2x). The extracts were washed with water (2x), dried over sodium sulfate, filtered, and concentrated to afford an oily residue which was dissolved in ethyl acetate (4 mL). This solution was mixed with 4N HCl in 1,4-dioxane (2 mL) followed by addition of diethyl ether until precipitation of product occurred. The desired product was obtained by filtration to afford 0.7 g (53%). LC/MS: t_R = 0.96 min, 358.16 $(MH)^+$.

3-Piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine-2,2-dioxide



3-(1-Benzyl-piperidin-4-yl)-3,4-dihydro-1H-benzo[1,2,6]thiadiazine-2,2-dioxide (0.46 g, 1.29 mmol) in methanol (10 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 46 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 0.26 g (75%) of the desired material. ^{1}H-NMR (CD_3OD) δ 1.53-1.61 (m, 2H), 1.80 (m, 2H), 2.55 (m, 2H), 2.95-3.05 (m, 2H), 3.30 (m, 2H), 3.70 (m, 2H), 4.65 (s, 2H), 6.70 (d, *J*=7.9, 1H), 7.40 (dd, J=8.2, 6.7, 1H), 7.10 (m, 2H). Mass spec.: 268.10 $(MH)^+$.

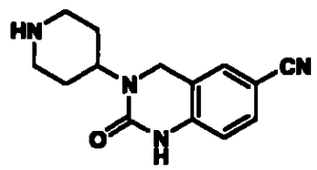
6-Bromo-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one



3-Piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (0.2 g, 0.87 mmol) was dissolved in acetic acid (2 mL). To this solution was added a solution of bromine (1.8 mL, 35.14 mmol) in acetic acid (0.5 mL) dropwise over 5 min. After stirring for at room temperature for 1 h, the reaction mixture was diluted with methylene chloride, washed with water (2x), brine (2x), dried over sodium sulfate, filtered, and

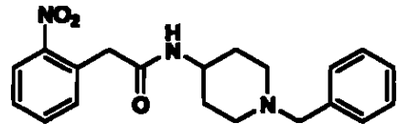
concentrated to afford 0.16 g (59%) which was used immediately without further purification. LC/MS: t_R = 0.91 min, 310.15 $(MH)^+$.

2-Oxo-3-piperidin-4-yl-1,2,3,4-tetrahydro-quinazoline-6-carbonitrile



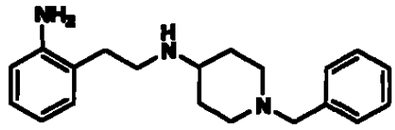
6-Bromo-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (0.16 g, 0.52 mmol), zinc cyanide (37 mg, 0.31 mmol) and tetrakis(triphenylphosphine)palladium(0) (60 mg, 0.05 mmol) were combined in dimethylformamide (4 mL). The reaction flask was connected to high vacuum and degassed (3x) by a freeze-thawing method, before being heated at 90°C with stirring under nitrogen for 1 h. After cooling to room temperature, the solution was evaporated *in vacuo* and the crude mixture purified by preparative HPLC to afford 50 mg (38%) of the desired nitrile. ^{1}H-NMR (CD_3OD) δ 1.99 (m, 2H), 2.08-2.23 (m, 2H), 3.15 (m, 2H), 3.50 (bs, 1H), 3.55 (bs, 1H), 4.40 (m, 1H), 4.47 (s, 2H), 6.93 (d, *J*=8.1, 1H), 4.10 (m, 2H). Mass spec.: 257.13 $(MH)^+$.

N-(1-Benzyl-piperidin-4-yl)-2-(2-nitro-phenyl)-acetamide



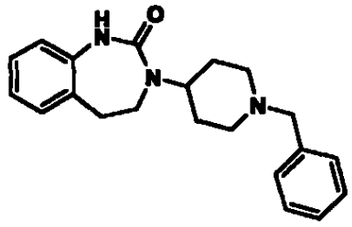
(2-Nitro-phenyl)-acetic acid (2.0 g, 11.04 mmol), 4-amino-1-benzylpiperidine (2.25 mL, 10.03 mmol), 1-hydroxybenzotriazole (1.49 g, 11.04 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (2.3 g, 12.03 mmol) were combined in ethyl acetate (25 mL). To this solution was added triethylamine (4.2 mL. 30.1 mmol) and the reaction mixture stirred at 40°C for 2 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with water (2x), 5% sodium bicarbonate, brine (2x), dried over sodium sulfate, and concentrated to afford 3.5 g (98%) of the desired product. LC/MS: t_R = 1.24 min, 354.30 $(MH)^+$.

[2-(2-Amino-phenyl)-ethyl]-(1-benzyl-piperidin-4-yl)-amine



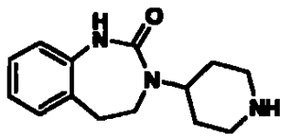
Into a flame dried flask, *N*-(1-benzyl-piperidin-4-yl)-2-(2-nitro-phenyl)-acetamide (3.2 g, 9.06 mmol) and lithium aluminium hydride (1.0 g, 18.12 mmol) were combined. 1,4-Dioxane (15 mL) was added and the mixture slowly brought to reflux over 1 h and stirred at reflux for 16 h. The reaction mixture was cooled to 0°C and excess lithium aluminium hydride destroyed by dropwise addition of methanol, followed by careful addition of 20% potassium hydroxide. The aluminum salts were filtered, the filtrate concentrated and used as is for the next reaction.

3-(1-Benzyl-piperidin-4-yl)1,3,4,5-tetrahydro-benzo[d][1,3]diazepin-2-one



A stirred solution of [2-(2-amino-phenyl)-ethyl]-(1-benzyl-piperidin-4-yl)-amine (0.44 g, 1.42 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with carbonyl diimidazole (0.23 g, 1.42 mmol). The reaction was stirred for 30 min at 0°C and at reflux for 1 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column to afford 100 mg (21%) of the desired product. LC/MS: t_R = 1.29 min, 336.34 $(MH)^+$.

3-Piperidin-4-yl-1,3,4,5-tetrahydro-benzo[d][1,3]diazepin-2-one

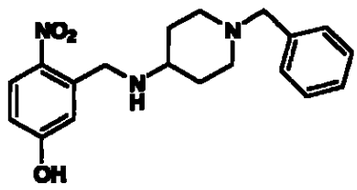


3-(1-Benzyl-piperidin-4-yl)1,3,4,5-tetrahydro-benzo[d][1,3]diazepin-2-one (100 mg, 0.3 mmol) in methanol (5 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 10 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen,

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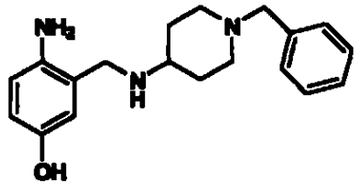
filtered through celite, and concentrated. Column chromatography gave 50 mg (68%) of the desired material. LC/MS: t_R = 1.07 min, 246.26 $(MH)^+$.

3-[(1-Benzyl-piperidin-4-yl-amino)-methyl]-4-nitro-phenol



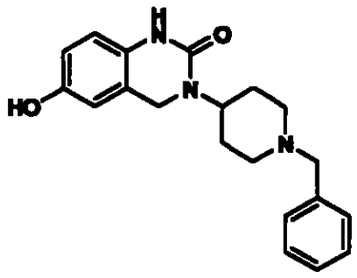
5-Hydroxy-2-nitro-benzaldehyde (5 g, 29.9 mmol) and 4-amino-1-benzylpiperidine (5.6 mL, 29.9 mmol) were combined in ethanol (30 mL). The resulting suspension was stirred at room temperature for 20 min before a solution of sodium borohydride (1.13 g, 29.9 mmol) in ethanol (10 mL) was added dropwise over 10 min. After the addition was complete, the reaction was stirred at room temperature for 1 h, cooled to 0°C and concentrated ammonium chloride added to the reaction mixture until no bubbling was observed. The solvents were evaporated *in vacuo* and the resultant crude mixture was dissolved in water (30 mL) and methylene chloride (40 mL). The layers were separated and the organic layer washed with water (2x), brine (2x), dried over sodium sulfate, filtered, and concentrated to afford 5.8 g (57%) of the desired product. LC/MS: t_R = 0.95 min, 342.27 $(MH)^+$.

4-Amino-3-[(1-benzyl-piperidin-4-yl-amino)-methyl]-phenol



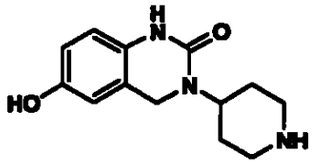
(1-Benzyl-piperidin-4-yl)-(2-nitro-benzyl)-amine (0.25 g, 0.7 mmol) and zinc dust (0.2 g, excess) were combined in 75% aqueous acetic acid (8 mL) and stirred at 60°C for 2 h. After cooling to room temperature, the solvents were removed *in vacuo* and the resultant crude mixture dissolved in water (10 mL), followed by addition of ammonium hydroxide until pH 3 was attained. The solution was extracted with methylene chloride (3x). The organic layers were pooled together, washed with water (2x), brine (2x), dried over sodium sulfate, filtered, and concentrated to afford 0.18 g (79%) of the desired product.

3-(1-Benzyl-piperidin-4-yl)-6-hydroxy-3,4-dihydro-1H-quinazolin-2-one



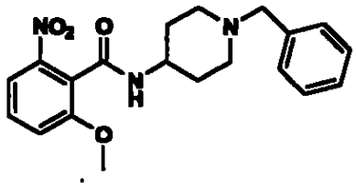
A stirred solution of 4-amino-3-[(1-benzyl-piperidin-4-yl-amino)-methyl]-phenol (0.16 g, 0.51 mmol) in tetrahydrofuran (3 mL) at 0°C was treated with carbonyl diimidazole (52 mg, 0.51 mmol). The reaction was stirred for 30 min at 0°C and at reflux for 1 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column to afford 100 mg (57%) of the desired product. LC/MS: t_R = 1.09 min, 338.28 $(MH)^+$.

6-Hydroxy-3 -piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one



3-(1-Benzyl-piperidin-4-yl)-6-hydroxy-3,4-dihydro-1H-quinazolin-2-one (100 mg, 0.3 mmol) in methanol (5 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 10 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 60 mg (81%) of the desired material. LC/MS: t_R = 0.75 min, 248.22 $(MH)^+$.

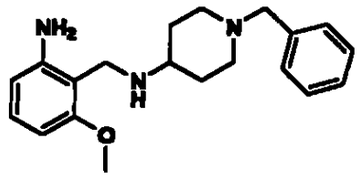
N-(1-Benzyl-piperidin-4-yl)-2-methoxy-6-nitro-benzamide



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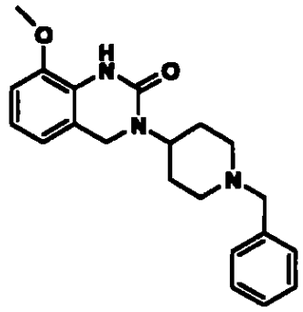
2-Methoxy-6-nitro-benzoic acid (2.0 g, 10.1 mmol), 4-amino-1-benzylpiperidine (1.9 mL, 10.1 mmol), 1-hydroxybenzotriazole (1.43 g, 10.5 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.9 g, 10.1 mmol) were combined in ethyl acetate (25 mL). To this solution was added triethylamine (4.2 mL, 30.3 mmol) and the reaction mixture stirred at 40°C for 2 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with water (2x), 5% sodium bicarbonate, brine (2x), dried over sodium sulfate, and concentrated to afford 3.2 g (86%) of the desired product. LC/MS: t_R = 1.10 min, 370.28 $(MH)^+$.

(2-Amino-6-methoxy-benzyl)-(1-benzyl-piperidin-4-yl)-amine



Into a flame dried flask, *N*-(1-benzyl-piperidin-4-yl)-2-methoxy-6-nitro-benzamide (1.0 g, 2.8 mmol) and lithium aluminium hydride (0.31 g, 8.45 mmol) were combined. To the mixture was added anhydrous 1,4-dioxane (15 mL). The mixture was slowly brought to reflux over 1 h and stirred at reflux for 16 h. The reaction mixture was cooled to 0°C and excess lithium aluminium hydride destroyed by dropwise addition of methanol, followed by careful addition of 20% potassium hydroxide. The aluminum salts were filtered, the filtrate concentrated and used as is for the next reaction.

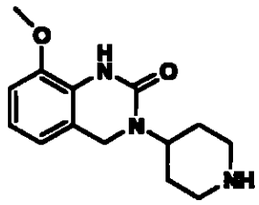
3-(1-Benzyl-piperidin-4-yl)-8-methoxy-3,4-dihydro-1H-quinazolin-2-one



A stirred solution of (2-amino-6-methoxy-benzyl)-(1-benzyl-piperidin-4-yl)-amine (0.2 g, 0.62 mmol) in tetrahydrofuran (3 mL) at 0°C was treated with carbonyl

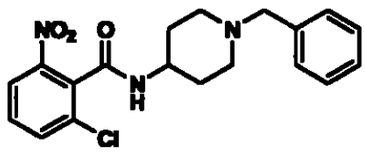
diimidazole (99 mg, 0.62 mmol). The reaction was stirred for 30 min at 0°C and at reflux for 1 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column to afford 150 mg (68%) of the desired product. LC/MS: t_R = 1.41 min, 352.30 $(MH)^+$.

8-Methoxy-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one



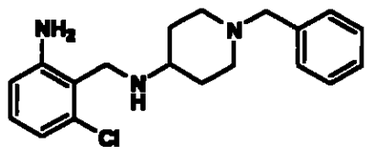
3-(1-Benzyl-piperidin-4-yl)-8-methoxy-3,4-dihydro-1H-quinazolin-2-one (100 mg, 0.28 mmol) in methanol (5 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 10 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 68 mg (93%) of the desired material. LC/MS: t_R = 1.11 min, 262.23 $(MH)^+$.

N-(1-Benzyl-piperidin-4-yl)-2-chloro-6-nitro-benzamide



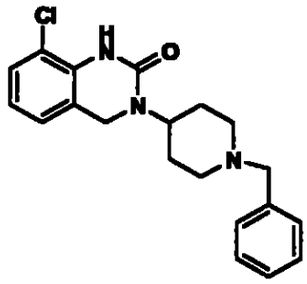
2-Chloro-6-nitro-benzoic acid (1.2 g, 5.97 mmol), 4-amino-1-benzylpiperidine (1.1 mL, 5.97 mmol), 1-hydroxybenzotriazole (0.84 g, 1.05 equiv) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (1.1 g, 1.05 equiv) were combined in ethyl acetate (20 mL). To this solution was added triethylamine (2.5 mL. 3.0 equiv) and the reaction mixture stirred at 40°C for 2 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with water (2x), 5% sodium bicarbonate, brine (2x), dried over sodium sulfate, and concentrated to afford 1.9 g (85%) of the desired product.

(2-Amino-6-chloro-benzyl)-(1-benzyl-piperidin-4-yl)-amine



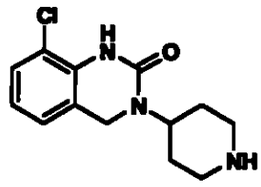
Into a flame dried flask, *N*-(1-benzyl-piperidin-4-yl)-2-chloro-6-nitro-benzamide (1.67 g, 4.47 mmol) and lithium aluminium hydride (0.51 g, 13.43 mmol) were combined. To this was added anhydrous 1,4-dioxane (15 mL). The mixture was slowly brought to reflux and stirred for 16 h. The reaction mixture was cooled to 0°C and excess lithium aluminium hydride destroyed by dropwise addition of methanol, followed by careful addition of 20% potassium hydroxide. The aluminum salts were filtered, the filtrate concentrated and used as is for the next reaction.

3-(1-Benzyl-piperidin-4-yl)-8-chloro-3,4-dihydro-1H-quinazolin-2-one



A stirred solution of (2-amino-6-chloro-benzyl)-(1-benzyl-piperidin-4-yl)-amine (0.66 g, 2.0 mmol) in tetrahydrofuran (8 mL) at 0°C was treated with carbonyl diimidazole (0.36 g, 2.05 mmol). The reaction was stirred for 30 min at 0°C and at reflux for 1 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column to afford 0.58 g (82%) of the desired product. LC/MS: t_R = 1.40 min, 356.25 $(MH)^+$.

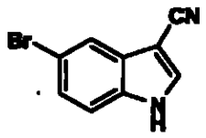
2-Chloro-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one



3-(1-Benzyl-piperidin-4-yl)-8-chloro-3,4-dihydro-1H-quinazolin-2-one (0.17 g, 0.48 mmol) in methanol (10 mL) was flushed with nitrogen, and treated with palladium on

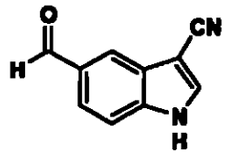
charcoal (10%, 17 mg). Trifluoroacetic acid (0.2 mL) was added and the mixture flushed with nitrogen then allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 100 mg (79%) of the desired material. LC/MS: $t_R = 0.99$ min, 266.08 $(MH)^+$.

5-Bromo-1H-indole-3-carbonitrile



A mixture of 5-bromo-indole-3-carboxaldehyde (5 g, 22.3 mmol), diammonium hydrogen phosphate (15.6 g, 31.8 mmol) in 1-nitropropane (66 mL) and acetic acid (22 mL) were heated at reflux for 16 h. After cooling to room temperature, the solvents were removed under reduced pressure and water added to the dark residue. After a short while, 5-bromo-1H-indole –3-carbonitrile precipitated rapidly. The solid was filtered, washed severally with water and dried for several hours to afford 4.3 g (86%) of the desired product. ^{1}H-NMR (CD_3OD) δ 7.40 (m, 2H), 7.77 (s, 1H), 7.97 (s, 1H). Mass spec.: 222.95 $(MH)^+$.

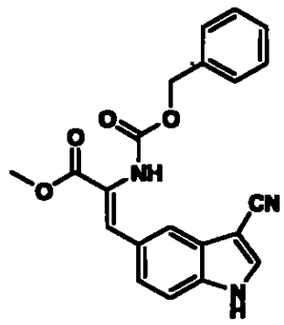
5-Formyl-1H-indole-3-carbonitrile



5-Bromo-1H-indole –3-carbonitrile (4.25 g, 19.23 mmol) and sodium hydride (0.51 g, 21.2 mmol) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (24 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -78°C and a solution of *sec*-butyllithium in cyclohexane (1.4M, 30.2 mL, 2.2 equiv) was added over several minutes. After 1 h at -78°C, dimethylformamide (6.0 mL) was slowly added and the mixture allowed to warm to room temperature overnight. The solution was cooled to 0°C and carefully treated with 1 N

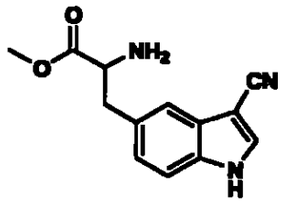
hydrochloric acid (45 mL). After a few minutes, solid sodium bicarbonate was added until a pH of 9-10 was attained. The two layers were separated and the aqueous phase washed twice with ethyl acetate. The combined organic layers were washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 2.4 g (72%) of pure material. LC/MS: t_R = 0.99 min, 171.07 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(3-cyano-1H-indol-5-yl)-acrylic acid methyl ester



A stirred solution of *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (1.68 g, 5.1 mmol) in tetrahydrofuran (10 mL) at room temperature was treated with tetramethylguanidine (0.6 mL, 1.1 equiv). After 10 min, 5-formyl-1H-indole-3-carbonitrile (0.72 g, 4.24 mmol) was added. After stirring at room temperature for 3 days, the solvent was evaporated and the residue washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 1.3 g (82%) of pure material. LC/MS: t_R = 1.43 min, 376.22 $(MH)^+$.

(±)-2-Amino-3-(3-cyano-1H-indol-5-yl)-propionic acid methyl ester

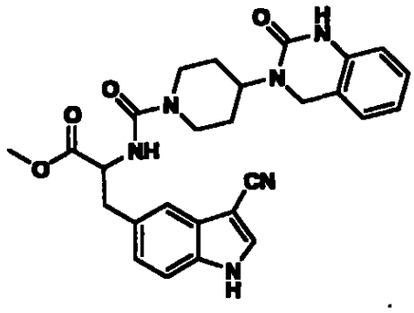


2-Benzyloxycarbonylamino-3-(3-cyano-1H-indol-5-yl)-acrylic acid methyl ester (0.5 g, 1.3 mmol) in methanol (8 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 50 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed

with nitrogen, filtered through celite, and concentrated. Column chromatography gave 0.3 g (92%) of the desired material. LC/MS: t_R = 0.80 min, 244.20 $(MH)^+$.

Example 202

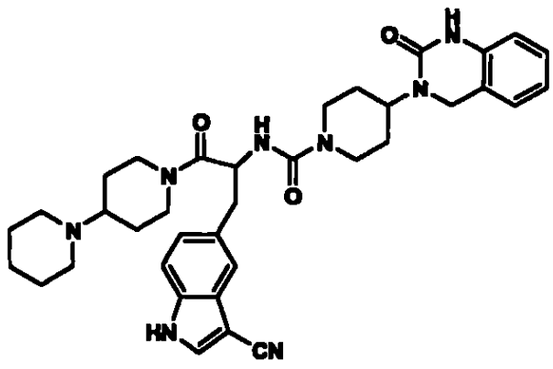
(±)-3-(3-Cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



A stirred solution of 2-amino-3-(3-cyano-1H-indol-5-yl)-propionic acid methyl ester (25 mg, 0.11 mmol) in tetrahydrofuran (3 mL) at 0°C was treated with carbonyl diimidazole (17.5 mg, 1.1 equiv.). The reaction was stirred for 5 min at 0°C, warmed to room temperature, stirred 10 min, and treated with 3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one (25 mg, 1.1 equiv.). The mixture was stirred at room temperature overnight. The solvent was evaporated and the residue purified by column chromatography to give 40 mg (75%) as a white powder. LC/MS: t_R = 1.37 min, 501.33 $(MH)^+$.

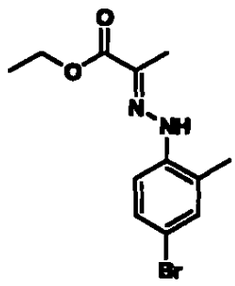
Example 203

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-cyano-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide



A solution of 3-(3-cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester (15 mg, 0.03 mmol) in methanol (0.6 mL) at room temperature was treated with a solution of lithium hydroxide monohydrate (3.0 mg, 2.5 equiv.) in water (0.1 mL). The solution was stirred at room temperature for 2 h. The solution was cooled to 0°C, and treated with aqueous 1M potassium hydrogen sulfate (60 µL, 2.0 equiv.), and the solvents evaporated to give the crude acid which was used immediately without purification. The crude acid was dissolved in dimethylformamide (0.4 mL) cooled to 0°C, and sequentially treated with methylene chloride (0.2 mL), 4-piperidyl-piperidine (11 mg, 2.2 equiv), *N,N*-diisopropylethylamine (12 µL, 2.3 equiv) and PyBop (19 mg, 1.2 equiv). The solution was stirred for 15 min at 0°C, warmed to room temperature, stirred 1.5 h, and concentrated. The product was purified by column chromatography to give 10.1 mg (52% 2 steps). ^{1}H-NMR (CD_3OD) δ 1.60-2.10 (m, 14H), 2.53 (d, *J*=13.0, 1H), 2.58 (d, *J*=12.2, 1H), 2.65-3.00 (m, 7H), 3.12 (d, *J*=7.0, 1H), 3.17 (d, *J*=7.0, 1H), 3.84 (s, 1H), 3.46 (bs, 1H), 4.08-4.86 (m, 5H), 4.70 (m, 1H), 5.02 (dd, *J*=8.2, 6.7, 1H), 6.79 (d, *J*=7.6, 1H), 6.9(m, 1H), 7.10 (dd, *J*=7.3, 7.9, 1H), 9.18 (s, 1H), 7.15 (dd, *J*=7.3, 7.6, 1H), 7.30 (m, 1H), 7.50 (m, 1H), 8.00 (s, 1H). Mass spec.: 647.41 $(MH)^+$.

3-(4-Bromo-2-methyl-phenylamino)-2-methyl-acrylic acid ethyl ester

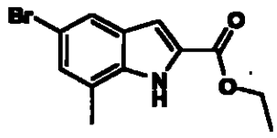


To a solution of 4-bromo-2-methyl aniline (7.0 g, 37.8 mmol) in acetonitrile (80 mL) was added, sequentially, concentrated hydrochloric acid (15 mL), water (40 mL) and a solution of sodium nitrite (2.74 g, 39.7 mmol) in water (40 mL) under ice cooling to give the diazonium salt. The solution was transferred dropwise to a solution of 50% potassium hydroxide (16 mL) and ethyl-2-methyl acetoacetate (5.38 mL, 38 mmol) in ethanol (50 mL) at 0°C. After the addition was complete, the

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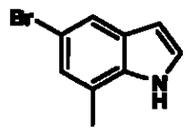
reaction mixture was poured into ice-water (150 mL) and extracted with ethyl acetate. The organic layer was washed with brine (2x), dried over sodium sulfate, filtered, and concentrated to give 7.5 g (66%) of the title compound which was used immediately without purification. ^{1}H-NMR (CD_3OD) δ 1.80 (t, *J*=7.0, 3H), 2.13 (s, 3H), 2.29 (s, 3H), 4.26 (dd, *J*=5.8, 7.0, 1H), 4.30 (dd, *J*=5.8, 7.0, 1H), 7.26 (m, 2H), 7.43 (m, 1H). Mass spec.: 323.07 $(MNa)^+$.

5-Bromo-7-methyl-1H-indole-2-carboxylic acid ethyl ester



A solution of *p*-toluenesulfonic acid monohydrate (4.26 g, 75 mmol) in toluene (80 mL) was heated at reflux under a dean-stark water separator for 1.5 h. To this solution was added a solution of 5-bromo-7-methyl-1H-indole-2-carboxylic acid ethyl ester (7.5 g, 25.0 mmol) in toluene (40 mL) and the reaction mixture heated at reflux for 5 h. After cooling to room temperature, the reaction mixture was poured in to ice-water (120 mL) and extracted twice with ethyl acetate. The organic layers were pooled together and washed with sodium bicarbonate (2x), brine (2x), dried over sodium sulfate, filtered, and concentrated. Column chromatography on silica gel afforded 5.5 g (78%) of the title compound. ^{1}H-NMR (CD_3OD) δ 1.35 (t, *J*=7.0, 3H), 2.52 (s, 3H), 4.36 (q, *J*=7.0, 2H), 7.13 (s, 1H), 7.14 (s, 1H), 7.70 (s, 1H), 11.90 (s, 1H). Mass spec.: 284.09 $(MH)^+$.

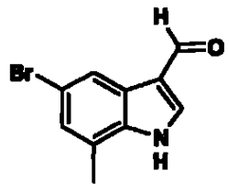
5-Bromo-7-methyl-1H-indole



5-Bromo-7-methyl-1H-indole-2-carboxylic acid ethyl ester (5.3 g, 18.7 mmol) was added to a potassium hydroxide solution in 1:1 water/ethanol mixture (20 mL) and heated at reflux for 12 h. After cooling to room temperature, the solvents were removed *in vacuo* and the resultant residue transferred to a 6N hydrochloric acid solution (20 mL). The white precipitate that formed was filtered, washed severally with water, and dried for several hours. The crude solid was dissolved in

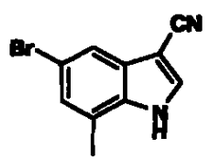
quinoline (14 mL) and heated at reflux for 4 h. After cooling to room temperature, the crude mixture was poured into a mixture of ice water (100 mL) and concentrated hydrochloric acid (16 mL), extracted with ethyl acetate (2x), brine (2x), dried over sodium sulfate, and concentrated. Attempts to recrystallize the desired product from isopropanol resulted in significant decomposition. The title compound was obtained by flash chromatography on silica get to afford 1.5 g (38%, 2 steps). LC/MS: t_R = 1.72 min, 210.05 $(MH)^+$.

5-Bromo-7-methyl-1H-indole-3-carboxaldehyde



5-Bromo-7-methyl-1H-indole (1.2 g, 5.71 mmol) was dissolved in acetonitrile (6 mL) and transferred slowly to a solution of bromomethylene dimethyl ammonium bromide (1.36 g, 6.28 mmol) in acetonitrile (9 mL) at –10°C to 0°C. The reaction was stirred at 0°C for 2 h and at room temperature for 30 min. The solvents were evaporated and the crude mixture dissolved in water and stirred at 50°C for 4 h. After cooling to room temperature, the crude mixture was extracted with ethyl acetate (2x). The organic layers were pooled together and washed with brine (2x), dried over magnesium sulfate, filtered, and concentrated. Purification by flash chromatography on silica gel afforded 0.7 g (52%, 2 steps) of the desired compound. ^{1}H-NMR (CD_3OD) δ 2.50 (s, 3H), 7.24 (s, 1H), 8.34 (m, 1H), 9.93 (s, 1H). Mass spec.: 238.05 $(MH)^+$

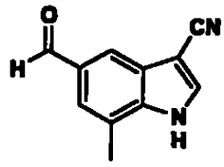
5-Bromo-7-methyl-1H-indole-3-carbonitrile



A mixture of 5-bromo-indole-3-carboxaldehyde (0.7 g, 2.94 mmol), diammonium hydrogen phosphate (2.05 g, 15.5 mmol) in 1-nitropropane (9 mL) and acetic acid (3 mL) were heated at reflux for 16 h. After cooling to room temperature,

the solvents were removed under reduced pressure and water added to the dark residue. After a short while, 5-bromo-1H-indole-3-carbonitrile precipitated rapidly, was filtered, washed severally with water and dried for several hours to afford 0.6 g (87%) of the desired nitrile. LC/MS: t_R = 1.71 min, 235.01 $(MH)^+$.

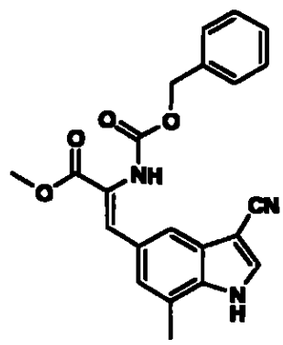
5-Formyl-7-methyl-1H-indole-3-carbonitrile



5-Bromo-7-methyl-1H-indole –3-carbonitrile (0.58 g, 2.46 mmol) and sodium hydride (68 mg, 2.7 mmol) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (9 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -78°C and a solution of *sec*-butyllithium in cyclohexane (1.4M, 3.8 mL, 2.2 equiv) was added over several minutes. After 1 h at -78°C, dimethylformamide (0.9 mL) was slowly added and the mixture allowed to warm to room temperature overnight. The solution was cooled to 0°C and carefully treated with 1N hydrochloric acid. After a few minutes, solid sodium bicarbonate was added until a pH of 9-10 was attained. The two layers were separated and the aqueous phase washed twice with ethyl acetate. The combined organic layers were washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 60 mg (14%) of desired product and 0.4 g of unreacted starting material. LC/MS: t_R = 1.21 min, 185.10 $(MH)^+$.

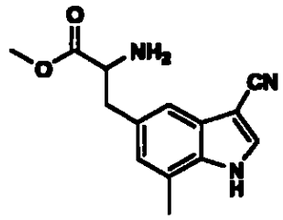
2-Benzyloxycarbonylamino-3-(3-cyano-7-methyl-1H-indol-5-yl)-acrylic acid methyl ester

224



A stirred solution of *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (180 mg, 0.54 mmol) in tetrahydrofuran (3 mL) at room temperature was treated with tetramethylguanidine (40 µL, 1.1 equiv). After 10 min, 5-formyl-7-methyl-1H-indole-3-carbonitrile (50 mg, 0.27 mmol) was added. After stirring at room temperature for 3 days, the solvent was evaporated and the residue washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 100 mg (95%) of pure material. LC/MS: t_R = 1.59 min, 390.24 $(MH)^+$.

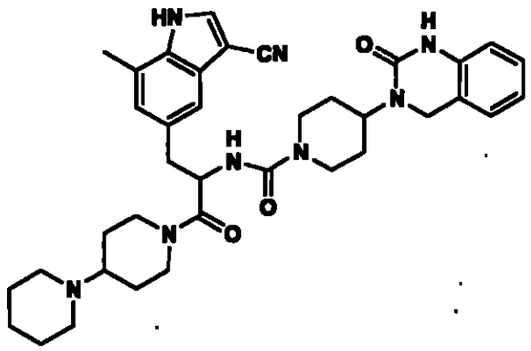
(±)-2-Amino-3-(3-cyano-7-methyl-1H-indol-5-yl)-propionic acid methyl ester



2-Benzyloxycarbonylamino-3-(3-cyano-7-methyl-1H-indol-5-yl)-acrylic acid methyl ester (0.1 g, 0.26 mmol) in methanol (2.5 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 10 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 60 mg (90%) of the desired material. LC/MS: t_R = 0.93 min, 258.22 $(MH)^+$.

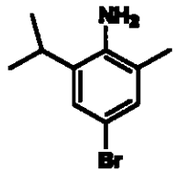
Example 204

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(3-cyano-7-methyl-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide



Prepared as describe above for Example 203: ^{1}H-NMR (CD_3OD) δ 1.55-2.10 (m, 16H), 2.50 (s, 3H), 2.80-3.20 (m, 9H), 4.10-4.40 (m, 7H), 4.90 (m, 3H), 6.72 (d, *J*=7.9, 1H), 6.93 (dd, *J*=8.5, 8.5, 1H), 7.40 (s, 1H), 7.88(s, 1H), 7.90 (s, 1H), 7.99 (s, 1H). Mass spec.: 651.57 $(MH)^+$.

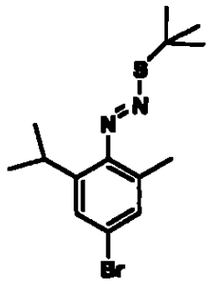
4-Bromo-2-isopropyl-6-methyl-phenylamine



2-Isopropyl-6-methyl-phenylamine (5 g, 33.5 mmol) was dissolved in acetic acid (20 mL). To this solution was added a solution of bromine (1.8 mL, 35.14 mmol) in acetic acid (5 mL) dropwise over 10 min. After stirring for 1 h at room temperature, the reaction mixture was diluted with methylene chloride, washed with water (2x), saturated sodium thiosulfate (2x), saturated sodium bicarbonate (2x), and brine. The organic phase was dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography on silica gel afforded 7.6 g (quantitative) of the desired product. LC/MS: t_R = 1.37 min, 230.07 $(MH)^+$.

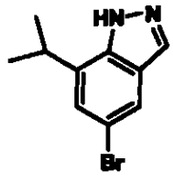
4-Bromo-2-isopropyl-6-methyl-phenyldiazo-t-butyl sulfide

226



4-Bromo-2-isopropyl-6-methyl-phenylamine (7.6 g, 33.5 mmol) was suspended in 24% hydrochloric acid (15 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (2.4 g, 1.05 equiv.) in water (5 mL), dropwise over 30 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (3.77 mL, 1.0 equiv.) in ethanol (25 mL) at 0°C over ca. 30 min. Following addition, the mixture was stirred at 0°C for 30 min and then crushed ice (ca. 50 mL) was added. The resulting light-brown solid was collected by filtration, washed with water, and dried under high vacuum for several hours to afford 7.9 g (72%) of the desired product. ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, *J*=6.7, 3H), 1.58 (s, 9H), 2.00 (s, 3H), 2.54 (m, 1H), 7.20 (s, 1H), 7.28 (s, 1H). Mass spec.: 331.08 $(MNa)^+$.

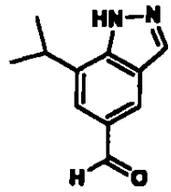
5-Bromo-7-isopropyl-1H-indazole



A flame-dried round bottom flask was charged with 4-bromo-2,6-diethylphenyldiazo-t-butyl sulfide (7.94 g, 24 mmol) and potassium t-butoxide (27 g, 10 equiv). A stir bar was added and the mixture placed under nitrogen. To this was added dry dimethylsulfoxide (70 mL). The mixture was stirred vigorously overnight at room temperature. The reaction mixture was carefully poured into a mixture of crushed ice (250 mL) and 10% hydrochloric acid (120 mL). The resulting suspension was collected by filtration and washed severally with water. The solid

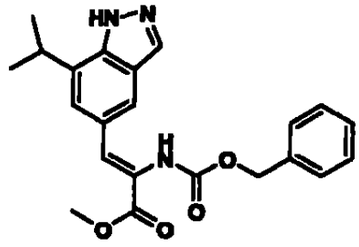
was collected and dried *in vacuo* to give 4.2 g (74%) of the desired product. LC/MS: t_R = 1.73 min, 241.06 $(MH)^+$.

7-Isopropyl-1H-indazole-5-carbaldehyde



5-Bromo-7-isopropyl-1H-indazole (3.1 g, 12.1 mmol) and sodium hydride (0.34 g, 1.1 equiv.) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (18 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -78°C and a solution of *sec*-butyllithium in cyclohexane (1.4M, 20 mL, 2.2 equiv.) was added over several minutes. After 1 h at -78°C, dimethylformamide (3.0 mL) was slowly added and the mixture allowed to warm to room temperature overnight. The solution was cooled to 0°C and carefully treated with 1 N hydrochloric acid (35 mL). After a few minutes, solid sodium bicarbonate was added until a pH of 9-10 was attained. The two layers were separated and the aqueous phase washed twice with ethyl acetate. The combined organic layers were washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 2.1 g (92%) of pure material. LC/MS: t_R = 1.15 min, 189.12 $(MH)^+$.

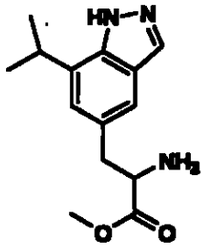
2-Benzyloxycarbonylamino-3-(7-isopropyl-1H-indazol-5-yl)acrylic acid methyl ester



A stirred solution of *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (0.39 g, 1.2 equiv) in tetrahydrofuran (5 mL) at room temperature was treated with tetramethylguanidine (0.16 mL, 1.1 equiv.). After 10 min, 7-isopropyl-1H-

indazole-5-carbaldehyde (0.2 g, 1.06 mmol) was added. After stirring at room temperature for 3 days, the solvent was evaporated and the residue purified by flash chromatography on silica gel to give 0.35 g (84%) of product. LC/MS: t_R = 1.61 min, 394.16 $(MH)^+$.

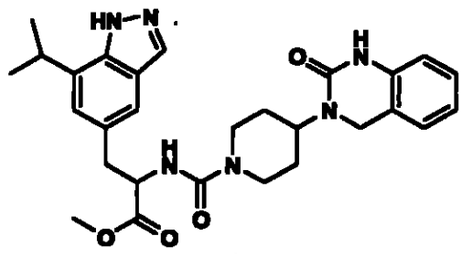
(±)-2-Amino-3-(7-isopropyl-1H-indazol-5-yl)propionic acid methyl ester



A solution of 2-benzyloxycarbonylamino-3-(7-isopropyl-1H-indazol-5-yl)acrylic acid methyl ester (0.35 g, 0.89 mmol) in methanol (7 mL) was flushed with nitrogen, and treated with palladium on charcoal (10%, 35 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 0.21 g (90%) of the desired material.

Example 205

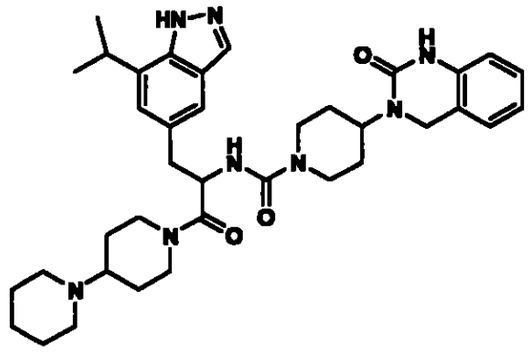
(±)-3-(7-Isopropyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



Prepared as described above for 3-(3-cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester. LC/MS: t_R = 1.49 min, 519.35 $(MH)^+$.

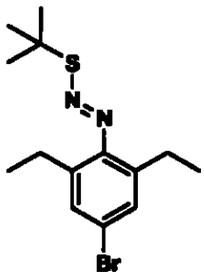
Example 206

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-isopropyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 203 from 3-(7-isopropyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester: ^{1}H-NMR (CD_3OD) δ 1.45 (m, 6H), 1.60-2.05 (m, 14H), 2.20-2.50 (m, 4H), 2.73 (d, *J*=13.7, 1H), 2.90 (m, 4H), 4.05 (d, *J*=14.0, 1H), 4.20 (m, 2H), 4.35 (s, 1H), 4.65 (dd, *J*=12.2, 14.3, 1H), 4.95 (m, 2H), 6.79 (d, *J*=7.9, 1H), 6.92 (dd, *J*=7.6, 6.1, 1H), 7.13(m, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 8.05(s, 1H). Mass spec.: 655.40 $(MH)^+$.

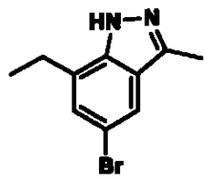
4-Bromo-2,6-diethylphenyldiazo-t-butyl sulfide



4-Bromo-2,6-diethylaniline (6.3 g, 27.6 mmol) was suspended in 24% hydrochloric acid (15 mL). The stirred mixture was cooled to -20°C and treated with sodium nitrite (2.0 g, 1.05 equiv.) in water (5 mL), dropwise over 30 min while the temperature was maintained below -5°C. After a further 30 min at -5°C to -20°C, the mixture was buffered to ca. pH 5 with solid sodium acetate. This mixture (kept at ca. -10°C) was added in portions to a stirred solution of t-butyl thiol (3.15 mL, 1.0 equiv.) in ethanol (25 mL) at 0°C over ca. 30 min. Following addition, the mixture was stirred at 0°C for 30 min and then crushed ice (ca. 50 mL) was added. The

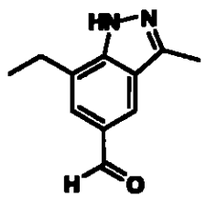
resulting light-brown solid was collected by filtration, washed with water, and dried under high vacuum for several hours to afford 6.0 g (66%) of the desired product. ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, *J*=7.6, 6H), 1.50 (s, 9H), 2.27 (m, 4H), 7.21 (s, 2H). Mass spec.: 331.08 $(MH)^+$.

5-Bromo-7-ethyl-3-methylindazole



A flame-dried round bottom flask was charged with 4-bromo-2,6-diethylphenyldiazo-t-butyl sulfide (4.0 g, 12.1 mmol) and potassium t-butoxide (13.2 g, 10 equiv). A stir bar was added and the mixture placed under nitrogen. To this was added dry dimethylsulfoxide (35 mL). The mixture was stirred vigorously overnight at room temperature. The reaction mixture was carefully poured into a mixture of crushed ice (130 mL) and 10% hydrochloric acid (60 mL). The resulting suspension was collected by filtration and washed severally with water. The solid was collected and dried *in vacuo* to give 2.85 g (98%) as a beige solid. ^{1}H-NMR (CD_3OD) δ 1.32 (t, *J*=7.6, 3H), 2.50 (s, 3H), 2.88 (m, 2H), 7.25 (s, 1H), 7.68 (s, 1H). Mass spec.: 239.26 $(MH)^+$.

7-Ethyl-3-methylindazole-5-carboxaldehyde

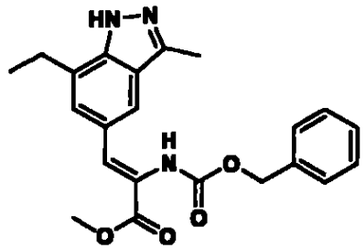


5-Bromo-7-ethyl-3-methylindazole (2.85 g, 11.9 mmol) and sodium hydride (0.31 g, 1.1 equiv.) were weighed into a flame-dried round-bottom flask containing a magnetic stir bar. Under a nitrogen atmosphere at room temperature, dry tetrahydrofuran (15 mL) was added. The mixture was stirred at room temperature for 15 min, during which time it became homogeneous. The stirred mixture was cooled to -78°C and a solution of *tert*-butyllithium in pentane (1.4M, 18.7 mL, 2.0 equiv)

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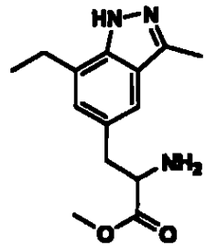
was added over several minutes. After 1 h at -78°C, dimethylformamide (2.8 mL) was slowly added and the mixture allowed to warm to room temperature overnight. The solution was cooled to 0°C and carefully treated with 1N hydrochloric acid (30 mL). After a few minutes, solid sodium bicarbonate was added until a pH of 9-10 was attained. The two layers were separated and the aqueous phase washed twice with ethyl acetate. The combined organic layers were washed with water (2x), brine (2x), dried over sodium sulfate, and concentrated. Column chromatography gave 1.5 g (67%) of pure material. LC/MS: t_R = 1.15 min, 189.12 $(MH)^+$.

2-Benzyloxycarbonylamino-3-(7-ethyl-3-methyl-1H-indazol-5-yl)-acrylic acid methyl ester



A stirred solution of *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (3.17 g, 9.57 mmol, 1.2 equiv.) in tetrahydrofuran (15 mL) at room temperature was treated with tetramethylguanidine (1.1 mL, 1.1 equiv.). After 10 min, 7-ethyl-3-methylindazole-5-carboxaldehyde (1.5 g, 7.98 mmol) was added. After stirring at room temperature for 3 days, the solvent was evaporated and the residue purified by flash chromatography on silica gel to give 2.5 g (80%) of product. LC/MS: t_R = 1.61 min, 394.16 $(MH)^+$.

(±)-2-Amino-3-(7-ethyl-3 methyl-1H-indazol-5-yl)-propionic acid methyl ester



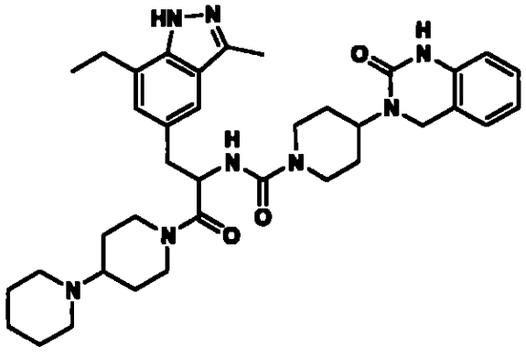
2-Benzyloxycarbonylamino-3-(7-ethyl-3-methyl-1H-indazol-5-yl)-acrylic acid methyl ester (1.0 g, 2.54 mmol) in methanol (15 mL) was flushed with nitrogen, and

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treated with palladium on charcoal (10%, 100 mg). The flask was flushed with hydrogen and allowed to stir under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Column chromatography gave 0.6 g (91%) of the desired material. ^{1}H-NMR (CD_3OD) δ 1.32 (m, 3H), 2.50 (s, 3H), 2.88 (dd, *J*=7.3, 7.6, 1H), 2.89 (dd, *J*=7.6, 7.6, 1H), 3.02 (dd, *J*=6.4, 7.0, 1H), 3.11 (dd, *J*=7.6, 5.8, 1H), 3.35 (s, 1H), 3.65 (m, 3H), 7.00 (s, 1H), 7.33 (s, 1H). Mass spec.: 262.24 $(MH)^+$.

Example 207

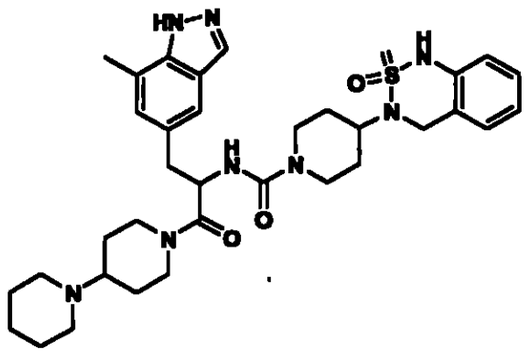
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 203 from (±)-2-amino-3-(7-ethyl-3 methyl-1H-indazol-5-yl)-propionic acid methyl ester. ^{1}H-NMR (CD_3OD) δ 1.35 (m, 3H), 1.85-2.20 (m, 4H), 2.50 (s, 1H), 2.70 (m, 2H), 2.85 (s, 3H), 2.88-3.25 (m, 7H), 3.35 (s, 1H), 3.47 (dd, *J*=7.3, 7.3, 1H), 4.00-4.40 (m, 7H), 4.70 (m, 1H), 5.00 (m, 3H), 6.79 (d, *J*=7.6, 1H), 6.93 (dd, *J*=7.3, 7.3, 1H), 7.10 (m, 1H), 7.15 (dd, *J*=7.3, 7.6, 1H), 7.45 (m, 1H). Mass spec.: 655.50 $(MH)^+$.

Example 208

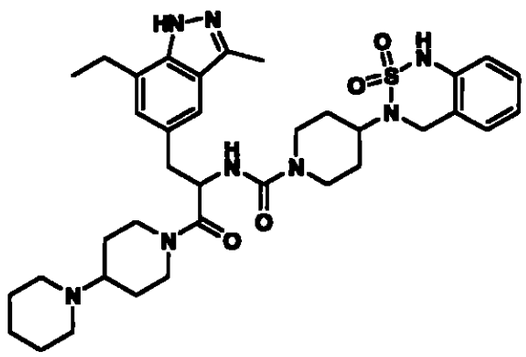
(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 203 from 3-piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine-2,2-dioxide: ^{1}H-NMR (CD_3OD) δ 1.20-2.10 (m, 12H), 2.20-2.60 (m, 6H), 2.90 (m, 6H), 3.78-4.11 (m, 4H), 4.60 (s, 3H), 4.90 (m, 1H), 6.70 (d, *J*=8.1, 1H), 6.79 (dd, *J*=7.67, 7.3, 1H), 7.44 (s, 1H), 7.10 (m, 1H), 7.13 (m, 3H), 8.03 (s, 1H). Mass spec.: 663.60 $(MH)^+$.

Example 209

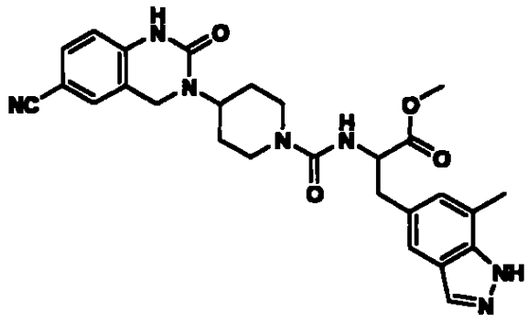
(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-3-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 203 from 3-piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine-2,2-dioxide: ^{1}H-NMR (CD_3OD) δ 1.35 (m, 3H), 1.42-2.05 (m, 10H), 2.40 (m, 3H), 2.55 (s, 3H), 2.67-3.12 (m, 7H), 3.85 (m, 1H), 3.97 (s, 1H), 4.03 (m, 3H), 4.65 (m, 4H), 4.95 (dd, *J*=4.9, 5.8, 1H), 6.73 (d, *J*=7.9, 1H), 6.98 (dd, *J*=7.3, 6.4, 1H), 7.20 (m, 2H), 7.88 (s, 1H). Mass spec.: 691.51 $(MH)^+$.

Example 210

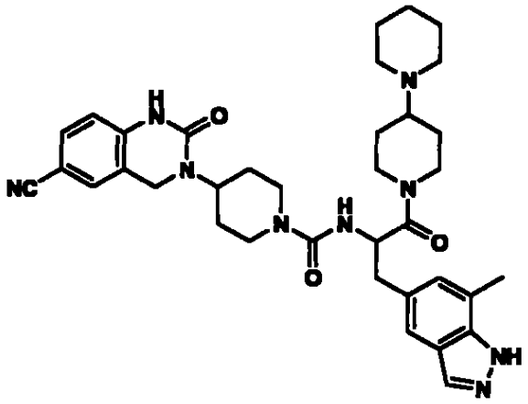
(±)-2-[4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carbonyl]-amino]-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester



Prepared as described above for 3-(3-cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester: LC/MS: t_R = 1.34 min, 516.40 $(MH)^+$.

Example 211

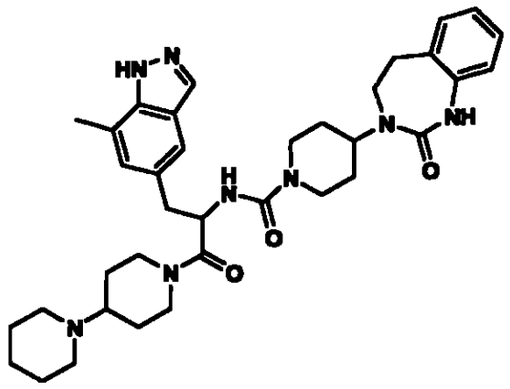
(±)-4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide



Prepared as described above for Example 203 from 2-oxo-3-piperidin-4-yl-1,2,3,4-tetrahydro-quinazoline-6-carbonitrile: ^{1}H-NMR (CD_3OD) δ 1.80 (m, 12H), 2.4 0(m, 4H), 2.60 (s, 3H), 2.70-3.20 (m, 10H), 4.00-4.30 (m, 6H), 5.00 (m, 1H), 5.50 (s, 2H), 6.90 (d, *J*=7.8, 1H), 7.21 (s, 1H), 7.50 (m, 4H), 8.05 (s, 1H). Mass spec.: 652.64 $(MH)^+$.

Example 212

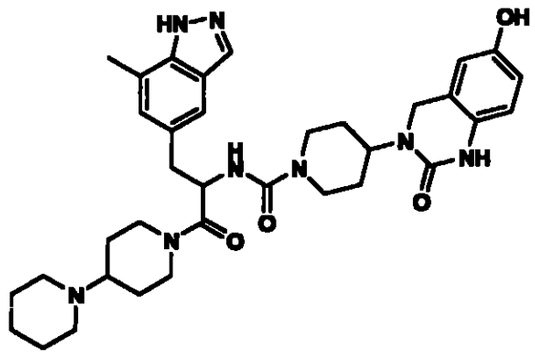
(±)-4-(2-Oxo-1,2,4,5-tetrahydro-benzo[d][1,3]diazepin-3-yl-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide



Prepared as described above for Example 203 from 3-piperidin-4-yl-1,3,4,5-tetrahydro-benzo[d][1,3]diazepin-2-one: ^{1}H-NMR (CD_3OD) δ 1.40-2.00 (m, 12H), 2.30-2.60 (m, 8H), 2.70-3.20 (m, 10H), 3.70 (m, 2H), 3.60 (d, *J*=9.5, 1H), 4.00-4.30 (m, 4H), 4.70 (m, 1H), 5.00 (m, 1H), 6.90 (m, 2H), 7.10 (m, 3H), 7.20 (s, 1H), 7.50 (s, 1H), 8.05 (s, 1H). Mass spec.: 652.64 $(MH)^+$.

Example 213

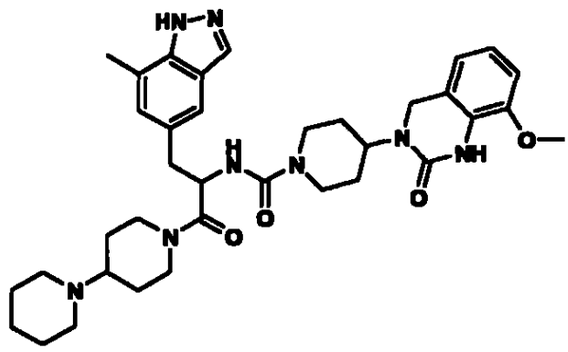
(±)-4-(6-Hydroxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide



Prepared as described above for Example 203 from 6-hydroxy-3 -piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one: LC/MS: t_R = 1.24 min, 643.62 $(MH)^+$.

Example 214

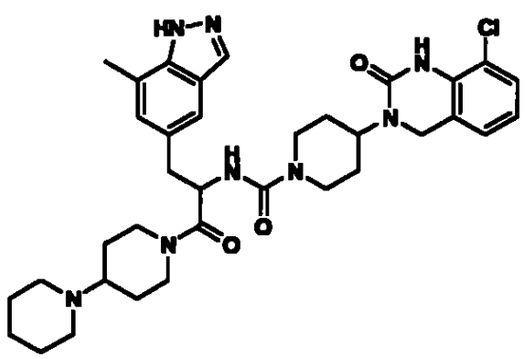
(±)-4-(8-Methoxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide



Prepared as described above for Example 203 from 8-methoxy-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one: ^{1}H-NMR (CD_3OD) δ 1.40-2.00 (m, 12H), 2.40 (m, 2H), 2.50 (s, 3H), 2.80 (m, 3H), 3.00-3.20 (m, 3H), 3.50 (m, 2H), 4.00-4.60 (m, 6H), 5.00 (m, 2H), 6.70 (dd, *J*=8.5, 10.1, 1H), 6.85 (m, 2H), 7.10 (m, 1H), 7.20 (s, 1H), 7.47 (s, 1H). Mass spec.: 657.41 $(MH)^+$.

Example 215

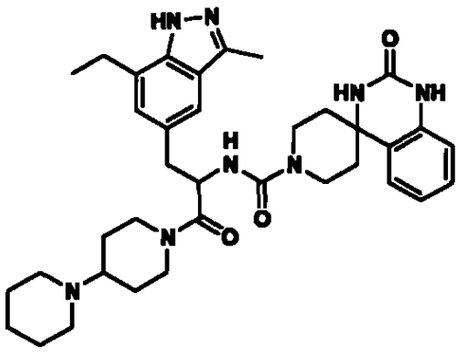
(±)-4-(8-Chloro-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide



Prepared as described above for Example 203 from 2-chloro-3-piperidin-4-yl-3,4-dihydro-1H-quinazolin-2-one: ^{1}H-NMR (CD_3OD) δ 1.40-2.00 (m, 14H), 2.30-2.60(m, 8H), 2.80 (m, 4H), 3.50 (m, 3H), 3.98 (s, 1H), 4.10 (m, 4H), 4.40 (m, 2H), 4.60 (m, 1H), 4.95 (m, 1H), 6.95 (dd, *J*=7.9, 7.9, 1H), 7.10 (m, 1H), 7.26 (dd, *J*=6.7, 7.6, 1H), 7.47 (m, 1H), 8.04 (s, 1H). Mass spec.: 661.27 $(MH)^+$.

Example 216

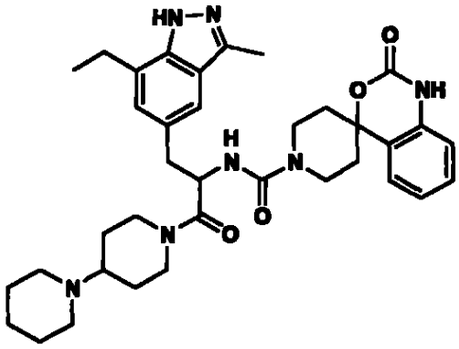
(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide



Prepared as described above for Example 203: LC/MS: t_R = 1.51 min, 641.63 $(MH)^+$.

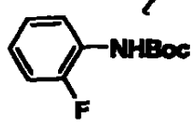
Example 217

(±)-*N*-(3-(7-Ethyl-3-methyl1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide



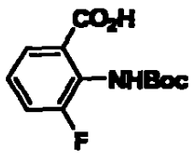
Prepared as described above for Example 203: LC/MS: t_R = 1.48 min, 642.61 $(MH)^+$.

tert-Butyl 2-fluorophenylcarbamate



To a solution of di-*tert*-butyldicarbonate (45.2 g, 207 mmol, 1.0 equiv.) in tetrahydrofuran (210 mL) at room temperature was added 2-fluoroaniline (20.0 mL, 207 mmol). The reaction was heated to reflux and held there for 6h. It was cooled, concentrated, dissolved in pentane, washed with 5% citric acid, then 1 M potassium bisulfate (2x), then water, then 20% potassium hydroxide, then brine, dried over magnesium sulfate, and concentrated to give 48.0 g (quant.) as an amber oil which was used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.52 (s, 9H), 6.68 (bs, 1H), 6.85-7.20 (m, 3H), 8.07 (dd, *J*=8.1, 8.1, 1H). Mass spec.: 234.18 $(MNa)^+$.

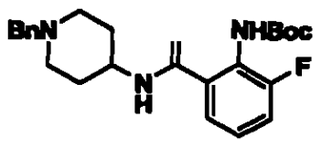
2-(*tert*-Butoxycarbonylamino)-3-fluoro-benzoic acid



To a solution of *tert*-butyl 2-fluorophenylcarbamate (44.0 g, 208 mmol) in tetrahydrofuran (660 mL) at -78°C was added *tert*-butyllithium in pentane (1.7 M, 306 mL, 2.5 equivx) dropwise. After addition was complete, the reaction was stirred at -78°C for 30 min. The solution was allowed to gradually reach -20°C before being recooled to -78°C and transferred via canula to a slurry of carbon dioxide (excess) and tetrahydrofuran (500 mL). The solution was allowed to slowly warm to room temperature. The reaction mixture was concentrated to remove most of the tetrahydrofuran, and poured into a sep funnel containing water and diethyl ether. The layers were separated, and the aqueous extracted with diethyl ether twice more. The ethereals were discarded. The aqueous was acidified with 5% citric acid, extracted with diethyl ether (3x). The ethereal was dried over magnesium sulfate, and concentrated to give a light yellow solid which was recrystallized from hot toluene to give 37.1 g (70%) as a faint yellow solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.50 (s, 9H), 6.25 (bs, 1H), 7.18 (ddd, *J*=7.9, 7.9, 4.9, 1H), 7.33 (dd, *J*=9.5, 9.2, 1H), 7.79 (d, *J*=7.9, 1H), 7.94 (s, 1H). Mass spec.: 278.21 $(MNa)^+$.

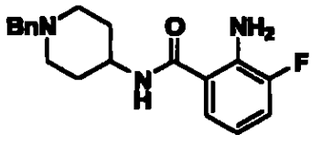
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tert-Butyl 2-(1-benzylpiperidin-4-ylcarbamoyl)-6-fluorophenylcarbamate



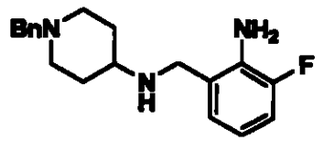
To a solution of 2-(*tert*-butoxycarbonylamino)-3-fluoro-benzoic acid (37.1 g, 145 mmol), 4-amino-1-benzylpiperidine (35.6 mL, 1.20 equiv.), 1-hydroxybenzotriazole (21.6 g, 1.1 equiv.), and triethylamine (44.1 g, 3.0 equiv.) in ethyl acetate (450 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30.7 g, 1.1 equiv.) in one portion. Initially, everything went into solution, but a precipitate formed very rapidly. The reaction was fitted with a reflux condenser and heated at reflux for 5 h. The reaction was diluted with ethyl acetate, washed with water (2x), then 1N sodium hydroxide (2x), then brine, dried over magnesium sulfate, and concentrated to give 67.0 g (quant.) as a white solid which was used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9H), 1.55 (m, 2H), 1.99 (bd, *J*=11.0, 2H), 2.17 (dd, *J*=11.0, 11.0, 2H), 2.84 (bd, *J*=11.3, 2H), 3.51 (s, 2H), 3.94 (m, 1H), 6.13 (bd, *J*=7.6, 1H), 7.10-7.28 (m, 4H), 7.31 (m, 4H), 7.59 (s, 1H). Mass spec.: 428.41 $(MH)^+$.

2-Amino-*N*-(1-benzylpiperidin-4-yl)-3-fluorobenzamide



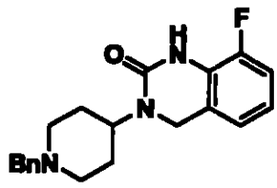
To a solution of *tert*-butyl 2-(1-benzylpiperidin-4-ylcarbamoyl)-6-fluorophenylcarbamate (67.0 g, 157 mmol) in dichloromethane (700 mL) at 0°C was added trifluoroacetic acid (100 mL). The ice bath was removed and the reaction stirred at room temperature overnight. The reaction was concentrated and partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous was extracted with ethyl acetate (2x), which were washed with water (3x), then brine, dried over magnesium sulfate, and concentrated to give 47.6 g (93%) as a white solid which was used without purification. Mass spec.: 328.33 $(MH)^+$.

N-(2-Amino-3-fluorobenzyl)-1-benzylpiperidin-4-amine



To a refluxing suspension of lithium aluminum hydride (16.1 g, 424 mmol, 3.50 equiv.) in dioxane (800 mL) was added a solution of 2-amino-*N*-(1-benzylpiperidin-4-yl)-3-fluorobenzamide (39.7 g, 121 mmol) in dioxane (250 mL) at such a rate that gas evolution was limited to a safe flow. Upon completion of the addition, the resulting suspension was heated at reflux for 4 h. The reaction was cooled to 0°C, and quenched by the cautious addition of 20% potassium hydroxide. Upon formation of a white, filterable precipitate, the solid was filtered through a course glass sintered funnel, and the eluent concentrated to give 36.3 g (96%) as a light yellow oil which was used without purification. Mass spec.: 314.29 $(MH)^+$.

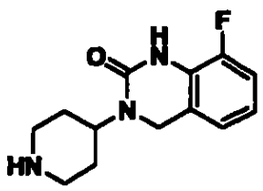
3-(1-Benzylpiperidin-4-yl)-8-fluoro-3,4-dihydroquinazolin-2(1H)-one



To a solution of *N*-(2-amino-3-fluorobenzyl)-1-benzylpiperidin-4-amine (36.3 g, 116 mmol) in tetrahydrofuran (600 mL) at room temperature was added carbonyl diimidazole (20.7 g, 1.10 equiv.) in one portion. The reaction was stirred at room temperature for 3 h, heated at reflux for 30 min, and concentrated. The resulting solid was dissolved in 1:1 diethyl ether/ethyl acetate, washed with water (3x), then brine, dried over magnesium sulfate, and concentrated to give the crude product as a wet, yellow solid. The solid was triturated with diethyl ether and filtered to give 30.0 g (76%) as a white powder. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.68 (m, 2H), 1.86 (dddd, *J*=11.9, 11.9, 11.9, 3.4, 2H), 2.14 (dd, *J*=11.6, 10.1, 2H), 2.98 (d, *J*=11.6, 2H), 3.51 (s, 2H), 4.34-4.44 (m, 3H), 6.71 (bs, 1H), 6.79-6.89 (m, 2H), 6.94 (dd, *J*=9.2, 9.2, 1H), 7.21-7.34 (m, 5H). Mass spec.: 340.30 $(MH)^+$.

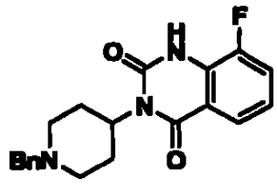
8-Fluoro-3,4-dihydro-3-(piperidin-4-yl)quinazolin-2(1H)-one

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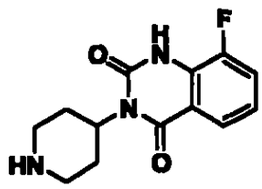
A 250 mL flask was charged with 3-(1-benzylpiperidin-4-yl)-8-fluoro-3,4-dihydroquinazolin-2(1H)-one (1.40 g, 4.12 mmol) and methanol (25.0 mL). The suspension was heated with a heat gun to aid in dissolution. The flask was flushed with nitrogen, treated with palladium on charcoal (141 mg, 0.032 equiv.), flushed with nitrogen, then hydrogen, and vigorously stirred under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated to give 0.99g (97%) as a white solid which was used without purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.71 (m, 4H), 2.75 (m, 2H), 3.16 (m, 2H), 4.38 (s, 2H), 4.46 (m, 1H), 6.77 (bs, 1H), 6.81-6.89 (m, 2H), 6.95 (m, 1H). Mass spec.: 250.22 $(MH)^+$.

3-(1-Benzylpiperidin-4-yl)-8-fluoroquinazoline-2,4(1H,3H)-dione



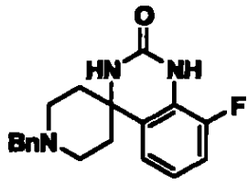
To a solution of 2-amino-*N*-(1-benzylpiperidin-4-yl)-3-fluorobenzamide (750 mg, 2.29 mmol) in dichloromethane (30.0 mL) at 0°C was added triphosgene (227 mg, 0.33 equiv.) as a solution in dichloromethane (5 mL). The ice bath was removed and the reaction heated at reflux for 6h. The reaction was concentrated, dissolved in ethyl acetate, washed with saturated sodium bicarbonate, then water, then brine, dried over magnesium sulfate, and concentrated to give 700 mg of a white solid. The crude product was purified by flash chromatography to give 205 mg (25%) as a white solid. Mass spec.: 354.13 $(MH)^+$.

8-Fluoro-3-(piperidin-4-yl)quinazoline-2,4(1H,3H)-dione



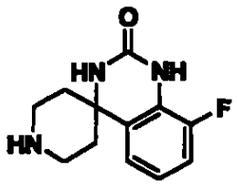
A flask containing a solution of 3-(1-benzylpiperidin-4-yl)-8-fluoroquinazoline-2,4(1H,3H)-dione (75.0 mg, 0.21 mmol) and palladium on charcoal (8.00 mg, 0.035 equiv) in methanol (3.00 mL) was flushed first with nitrogen, then hydrogen. The reaction was stirred under an atmosphere of hydrogen overnight. The reaction was flushed with nitrogen, filtered through celite, and concentrated to give 53 mg (95%) as a white solid which was used without purification. Mass spec.: 264.25 $(MH)^+$.

8'-Fluoro-2',3'-dihydro-2'-oxospiro-(1-phenylmethylpiperidine)-4,4'-quinazoline



A 500 mL 3-neck flask was charged with polyphosphoric acid (110 mL) and fitted with an overhead stirrer, a nitrogen inlet, and a bubbler. The flask was flushed with nitrogen and heated to 105°C in an oil bath. To this was added 1-benzyl-4-piperidone (21.0 mL, 115 mmol). To this was added *N*-(2-Fluorophenyl)urea (21.3 g, 1.2 equiv) in many small portions over 2h. The reaction was heated to 160°C with vigorous stirring. After 2h, the reaction was quenched by pouring over crushed ice and neutralizing with 20% potassium hydroxide. The reaction mixture was extracted with dichloromethane, washed with water, then brine, dried over magnesium sulfate, and concentrated. The whole lot was purified by preparative HPLC (~130 injections) to give a much purer product. The product was repurified by flash chromatography to give a solid which was triturated with diethyl ether and filtered to give 275 mg (0.7%) as a white solid. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.91 (dd, *J*=13.7, 2.1, 2H), 2.10 (ddd, *J*=13.1, 13.1, 4.3, 2H), 2.27 (ddd, *J*=12.5, 12.5, 2.1, 2H), 2.86 (m, 2H), 3.57 (s, 2H), 5.40 (bs, 1H), 6.90 (bs, 1H), 6.90-7.05 (m, 3H), 7.27 (m, 1H), 7.32 (m, 4H). Mass spec.: 326.13 $(MH)^+$.

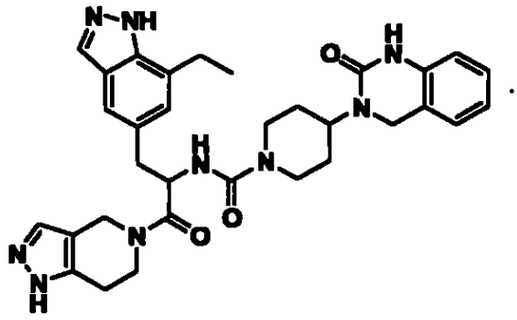
8'-Fluoro-2',3'-dihydro-2'-oxospiro-piperidine-4,4'-quinazoline



To a solution of 8'-fluoro-2',3'-dihydro-2'-oxospiro-(1-phenylmethylpiperidine)-4,4'-quinazoline (250 mg, 0.77 mmol) in methanol (4 mL) and dichloromethane (4 mL) was added palladium on charcoal (30.0 mg, 0.037 equiv.). The reaction was flushed with hydrogen, and stirred under an atmosphere of hydrogen overnight. The balloon was removed, the reaction flushed with nitrogen, filtered through celite, washed with additional methanol, and concentrated to give 158 mg (87%) as a white solid which was used without purification. ^{1}H-NMR ($CDCl_3/CD_3OD$, 500 MHz) δ 1.87 (d, *J*=12.8, 2H), 2.15 (ddd, *J*=14.0, 14.0, 5.5, 2H), 3.10 (m, 4H), 6.84 (m, 2H), 6.93 (d, *J*=7.0, 1H). Mass spec.: 236.11 $(MH)^+$.

Example 218

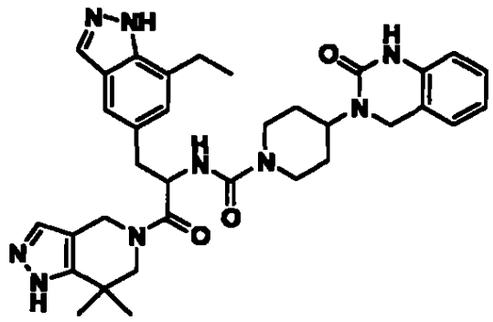
(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.24 (m, 2H), 1.55-2.07 (m, 5H), 2.57 (m, 1H), 2.82 (m, 4H), 3.08 (m, 2H), 3.30 (m, 3H), 3.35 (m, 5H), 3.48 (m, 3H), 3.65 (m, 1H), 4.14 (m, 2H), 4.27 (m, 2H), 4.33-4.57 (m, 2H), 5.06 (dd, *J*=6.7, 6.7, 1H), 5.22 (d, *J*=1.8, 2H), 6.78 (d, *J*=7.6, 1H), 6.93 (m, 1H), 7.00-7.18 (m, 3.5 H), 7.37 (d, *J*=9.8, 1H), 7.46 (s, 0.5H), 7.91 (dd, *J*=10.1, 1.8, 1H). Mass spec.: 596.43 $(MH)^+$.

Example 219

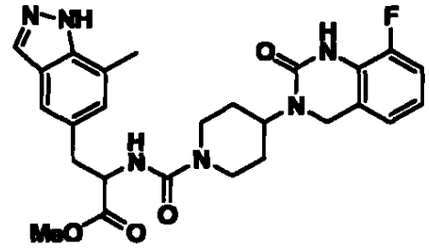
(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-7,7-dimethyl-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.11 (m, 3H), 1.50-1.80 (m, 4H), 2.87 (m, 4H), 3.10 (m, 2H), 3.32 (m, 9H), 3.48 (m, 4H), 4.00-4.45 (m, 6H), 5.05-5.25 (m, 2H), 6.77 (d, J=6.1, 1H), 6.93 (m, 1H), 7.13 (m, 3H), 7.30-7.60 (m, 2H), 7.95 (m, 1H). Mass spec.: 624.49 $(MH)^+$.

Example 220

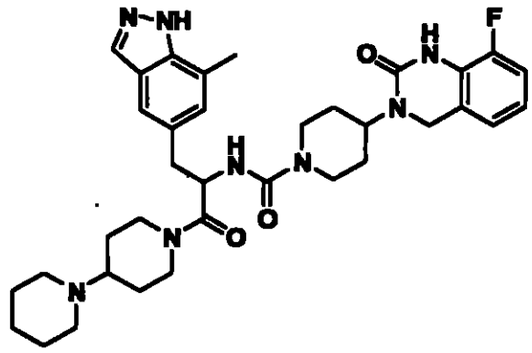
(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-methyl-1H-indazol-5-yl)propanoate



Prepared as described above for 3-(3-cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.53-1.68 (m, 4H), 2.48 (s, 3H), 2.82 (m, 2H), 3.05 (m, 6H), 3.09 (dd, J_{AB}=13.7, 6.1, 1H), 3.14 (dd, J_{AB}=14.0, 6.1, 1H), 3.35 (bs, 1H), 3.68 (s, 3H), 3.88-4.02 (m, 2H), 4.22 (d, J_{AB}=15.6, 1H), 4.25 (d, J_{AB}=15.3, 1H), 4.44 (m, 1H), 4.71 (dd, J=6.1, 6.1, 1H), 6.78 (d, J=7.3, 1H), 6.84 (ddd, J=7.6, 7.6, 4.9, 1H), 6.88-6.95 (m, 2H), 7.28 (s, 1H), 7.91 (s, 1H). Mass spec.: 509.25 $(MH)^+$.

Example 221

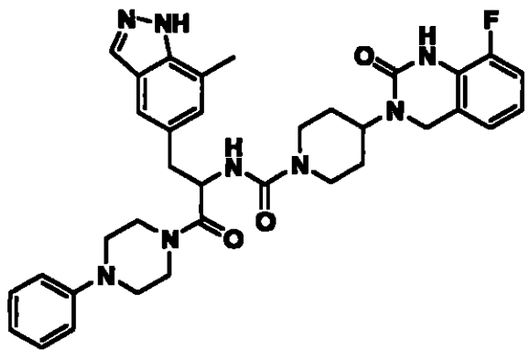
(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.25 (m, 1H), 0.82 (m, 1H), 1.25-2.10 (m, 13H), 2.20-2.63 (m, 6H), 2.68-2.98 (m, 4H), 3.00-3.22 (m, 3H), 3.31 (m, 2H), 3.44 (bs, 1H), 4.00-4.50 (m, 6H), 4.64 (m, 1H), 4.96 (m, 1H), 6.85-7.05 (m, 3H), 7.08 (s, 0.4H), 7.20 (s, 0.6H), 7.46 (d, *J*=7.0, 1H), 7.99 (s, 0.4H), 8.05 (d, *J*=2.4, 0.6H). Mass spec.: 645.58 $(MH)^+$.

Example 222

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide

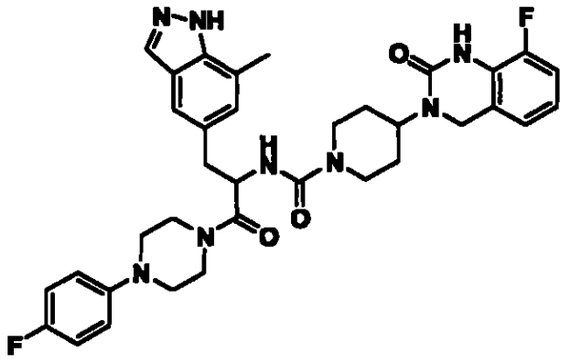


Prepared as described above for Example 203: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.73 (m, 4H), 2.49 (m, 4H), 2.80-3.26 (m, 7H), 3.43 (m, 2H), 3.65-3.95 (m, 3H), 4.14 (dd, *J*=21.7, 14.3, 2H), 4.32 (s, 2H), 4.51 (m, 1H), 5.15 (dd, *J*=7.9, 6.4, 1H), 5.90 (bs, 1H), 6.80 (d, *J*=7.3, 1H), 6.83-7.01 (m, 4H), 7.06 (dd, *J*=7.6, 7.3, 1H), 7.10 (s, 1H),

7.26-7.33 (m, 2H), 7.44 (s, 1H), 7.87 (s, 1H), 8.06 (s, 1H). Mass spec.: 639.36 $(MH)^+$.

Example 223

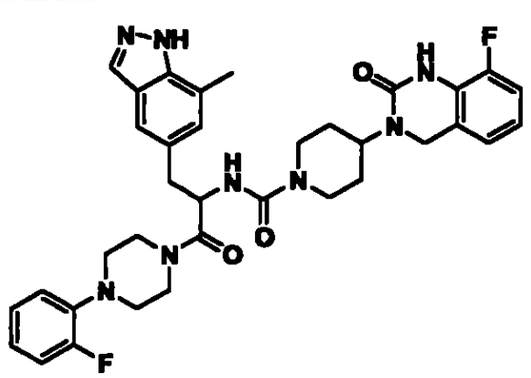
(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(4-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.73 (m, 4H), 2.26 (dd, *J*=7.9, 7.6, 1H), 2.49 (s, 3H), 2.75-3.05 (m, 4H), 3.09 (m, 2H), 3.19-3.45 (m, 3H), 3.63 (m, 1H), 3.78 (m, 2H), 4.13 (dd, *J*=16.5, 15.3, 2H), 4.32 (s, 2H), 4.50 (m, 1H), 5.15 (dd, *J*=8.2, 6.1, 1H), 5.85 (bs, 1H), 6.70-6.84 (m, 3H), 6.85-7.02 (m, 5H), 7.09 (s, 1H), 7.43 (s, 1H), 7.78 (s, 1H), 8.06 (s, 1H). Mass spec.: 657.35 $(MH)^+$.

Example 224

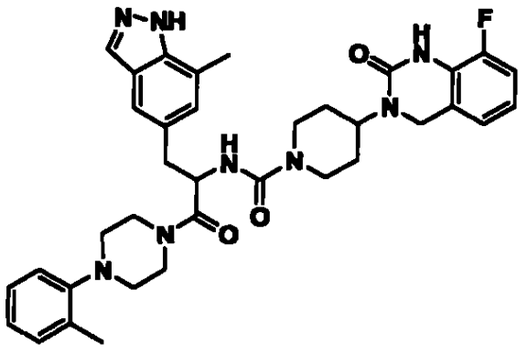
(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(2-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.62-1.78 (m, 4H), 2.24 (dd, *J*=7.9, 8.2, 1H), 2.50 (s, 3H), 2.70-2.85 (m, 2H), 2.85-2.96 (m, 2H), 2.00 (m, 1H), 3.08 (dd, J_{AB}=13.1, 8.6, 1H), 3.12 (m, 1H), 3.30 (m, 1H), 3.57 (m, 1H), 3.73 (m, 2H), 4.13 (dd, *J*=19.8, 15.0, 2H), 4.33 (s, 2H), 4.53 (m, 1H), 5.18 (dd, *J*=8.2, 5.8, 1H), 5.82 (bs, 1H), 6.58 (dd, *J*=8.2, 8.2, 1H), 6.81 (d, *J*=7.6, 1H), 6.85-7.05 (m, 5H), 7.09 (s, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 8.05 (s, 1H). Mass spec.: 657.37 $(MH)^+$.

Example 225

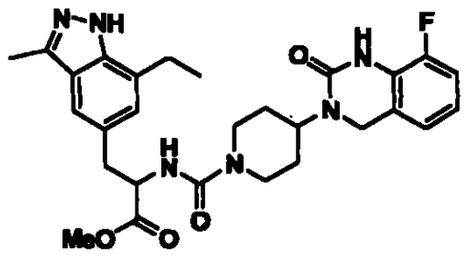
(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-o-tolylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.60-1.79 (m, 4H), 2.03 (dd, *J*=8.5, 8.2, 1H), 2.22 (s, 3H), 2.49 (s, 3H), 2.54 (dd, *J*=8.6, 8.5, 1H), 2.65 (m, 1H), 2.81 (m, 1H), 2.85-2.97 (m, 2H), 3.05-3.22 (m, 3H), 3.38 (m, 1H), 3.50-3.65 (m, 2H), 3.83 (m, 1H), 4.15 (dd, *J*=15.9, 15.3, 2H), 4.31 (s, 2H), 4.53 (m, 1H), 5.19 (dd, *J*=7.9, 5.8, 1H), 5.84 (bs, 1H), 6.54 (d, *J*=7.6, 1H), 6.81 (d, *J*=7.6, 1H), 6.89 (ddd, *J*=7.6, 7.6, 5.2, 1H), 6.96 (m, 2H), 7.00-7.23 (m, 4H), 7.39 (s, 1H), 7.43 (s, 1H), 8.04 (s, 1H). Mass spec.: 653.38 $(MH)^+$.

Example 226

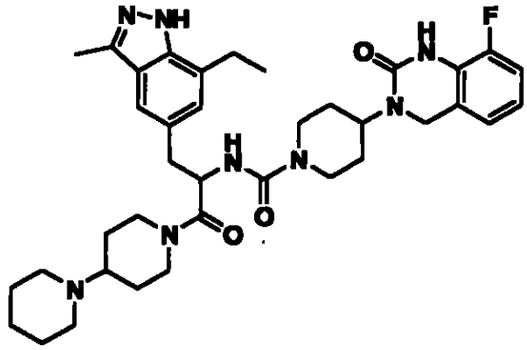
(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-ethyl-3-methyl-1H-indazol-5-yl)propanoate



Prepared as described above for 3-(3-cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester: ^{1}H-NMR (CD_3OD, 500 MHz) δ 1.33 (m, 3H), 1.39-1.72 (m, 4H), 2.70-2.95 (m, 3H), 3.06 (m, 1H), 3.25 (m, 1H), 3.70 (m, 3H), 3.95-4.30 (m 4H), 4.38 (m, 1H), 4.57 (m, 1H), 6.80-7.05 (m, 3H), 7.08 (s, 1H), 7.38 (s, 1H). Mass spec.: 537.47 $(MH)^+$.

Example 227

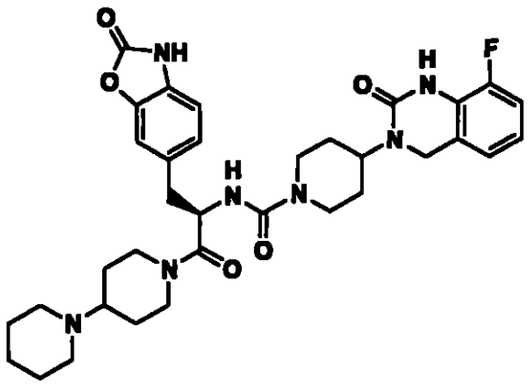
(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.36 (m, 1H), 0.70 (m, 1H), 1.21 (bd, *J*=11.9, 1H), 1.28-2.00 (m, 19H), 2.31 (dd, *J*=11.6, 11.3, 1H), 2.40 (dd, *J*=13.1, 11.6, 1H), 2.79-3.16 (m, 7H), 3.72 (m, 1H), 3.85-4.03 (m, 1H), 4.10-4.48 (m, 5H), 4.53 (bd, *J*=11.0, 1H), 5.05 (m, 1H), 6.85-7.03 (m, 3H), 7.08 (s, 0.2H), 7.18 (s, 0.8H), 7.37 (s, 1H). Mass spec.: 673.42 $(MH)^+$.

Example 228

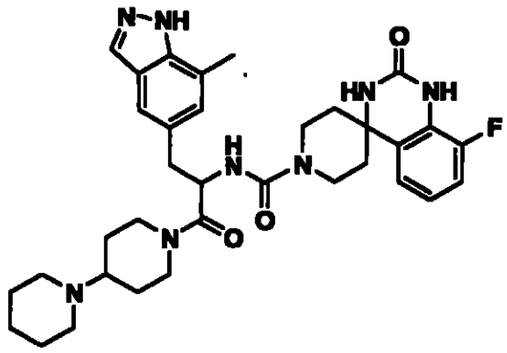
(R)-N-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ 0.71 (m, 1H), 1.26 (m, 1H), 1.40-2.15 (m, 13H), 2.50-3.29 (m, 9H), 3.32-3.64 (m, 3H), 4.14 (d, J_{AB}=12.8, 1H), 4.17 (d, J_{AB}=11.6, 1H), 4.32-4.45 (m, 3H), 4.68 (bd, J=13.4, 1H), 4.92 (m, 1H), 6.87-7.22 (m, 6H). Mass spec.: 648.47 $(MH)^+$.

Example 229

(±)-*N*-(3-(7-Methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-8'-fluoro-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide

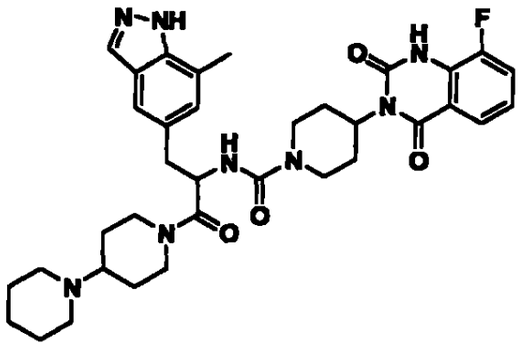


Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.23 (m, 1H), 0.85 (m, 1H), 1.20-2.10 (m, 22H), 2.25-2.55 (m, 7H), 2.58 (s, 3H), 2.74 (d, J=11.3, 1H), 2.94 (dd, J=12.5, 12.2, 2H), 3.00-3.20 (m, 5H), 3.40-3.65 (m, 2H), 3.80-4.15 (m, 4H), 4.55-4.73 (m, 2H), 4.96 (dd, J=7.9, 7.6, 1H), 5.01 (dd, J=10.4,

5.8, 1H), 6.65-7.15 (m, 5H), 7.21 (s, 1H), 7.47 (s, 1H), 7.96 (m, 1H), 8.04 (s, 1H). Mass spec.: 631.29 $(MH)^+$.

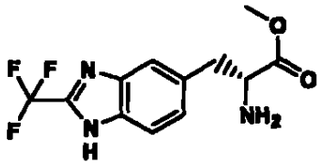
Example 230

(±)-4-(8-Fluoro-1,2-dihydro-2,4-dioxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide



Prepared as described above for Example 203: ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.26 (m, 1H), 0.81 (m, 1H), 1.20-2.10 (m, 11H), 2.20-2.80 (m, 9H), 2.90 (m, 3H), 3.10 (m, 3H), 3.34 (m, 1H), 3.44 (m, 1H), 4.06 (bd, J=13.4, 1H), 4.17 (d, J_{AB}=15.9, 1H), 4.22 (d, J_{AB}=13.1, 1H), 4.64 (dd, J=24.4, 13.1, 1H), 4.91-5.13 (m, 2H), 7.00-7.25 (m, 2H), 7.44 (m, 2H), 7.81 (m, 1H), 7.92-8.08 (m, 1H). Mass spec.: 659.59 $(MH)^+$.

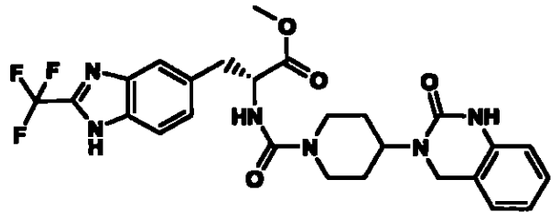
(*R*)-Methyl 2-amino-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate



A mixture of (*R*)-2-benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester (500 mg, 1.20 mmol) and trifluoroacetic acid (6 mL) was heated at 80°C for 16 h. The reaction mixture was poured into ice water (75 mL), neutralized to pH 7 with aqueous saturated sodium bicarbonate, and extracted with ethyl acetate (2 × 250 mL). The organic extracts were dried over sodium sulfate, filtered and evaporated to give the title compound as the trifluoroacetic acid salt (459 mg, 84 % yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.37 (bs, 1H) 7.35 (bs, 1H), 7.17 (d, J = 8.4

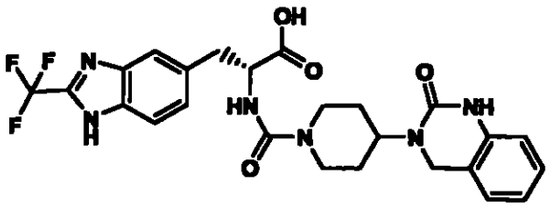
Hz, 1H), 4.70 (s, 2 H), 3.85 (dd, J = 8.4, 4.8 Hz, 1H), 3.77 (s, 3H), 3.30 (dd, J = 13.9, 4.8 Hz, 1H), 2.97 (dd, J = 13.5, 8.4 Hz, 1H). Mass spec.: 288 $(MH)^+$.

(*R*)-Methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate



A solution of the amino ester (R)-methyl 2-amino-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate (230 mg, 0.51 mmol), diisopropylethylamine (262 mg, 2.03 mmol), and disuccinimidyl carbonate (129 mg, 0.51 mmol) in a mixture of methylene chloride/dimethylformamide (15:1 ratio) was stirred at room temperature for 30 min. To the solution was added 4-(2-keto-1-benzimidazolinyl)piperidine and the reaction mixture was allowed to stir at room temperature for 16 h. The reaction mixture was filtered to remove any solids and was then purified by flash column chromatography (95:3:2 methylene chloride/methanol/triethylamine) to give the title compound (215 mg, 77 % yield) as a tan solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.21-7.16 (m, 1H), 7.05-6.94 (m, 3H), 6.70-6.68 (m, 2H), 5.11 (d, J = 7.3 Hz, 1H), 4.78 (dd, J = 12.1, 5.5 Hz, 1H), 4.42 (d, J = 4.4 Hz, 2H), 4.29 (d, J = 12.1 Hz, 1H), 3.82-3.72 (m, 2H), 3.74 (s, 3H), 3.44 (dd, J = 13.9, 5.5 Hz, 1H), 3.22 (dd, J = 13.9, 5.5 Hz), 2.95-2.83 (m, 3H), 2.18-2.03 (m, 2H), 1.79-1.68 (m, 2H). Mass spec.: 545 $(MH)^+$.

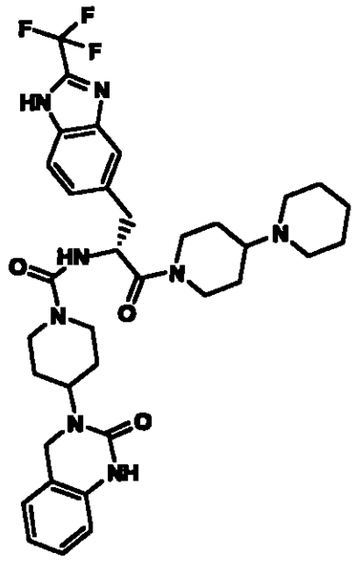
(*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid



To a solution of the ester (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate (220 mg, 0.40 mmol) in tetrahydrofuran and methanol (1:1 mixture, 20 mL) at 0°C was added lithium hydroxide (36 mg, 1.51 mmol) in water (10 mL). The mixture was stirred at 0°C for 2 h and then stored at -15°C for 16 h. The organic solvents were evaporated. The aqueous solution was extracted with ethyl acetate while adjusting the pH to 4 with 1N HCl (3 mL). The organic extracts were dried over sodium sulfate, filtered, and evaporated to give the title compound (176 mg, 82% yield). *LC/MS*: $t_R = 2.01$ min, 531 $(MH)^+$.

Example 231

N-((*R*)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide

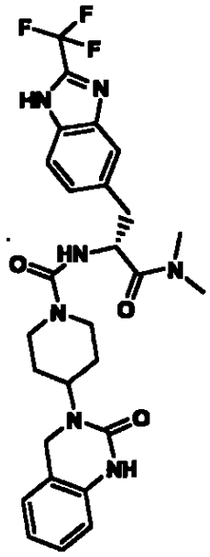


To a stirred solution of the acid (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid (33 mg, 0.06 mmol) and diisopropylethylamine (33 mg, 0.25 mmol) in methylene chloride (2 mL) was added a solution of PyBOP (33 mg, 0.06 mmol) and 4-piperidinopiperidine (12 mg, 0.07 mmol) in methylene chloride (1mL). The reaction mixture was stirred at room temperature for 16 h and was subjected to preparative thin layer chromatography for purification (1:10 2M ammonia in

methanol/methylene chloride) to give the title compound (4.6 mg, 12% yield). ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.73-7.71 (m, 1H), 7.62 (bs, 1H), 7.39-7.36 (m, 1H), 7.19-7.11 (m, 2H), 6.96 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 5.06-5.02 (m, 1H), 4.67-4.58 (m, 1H), 4.49-4.40 (m, 1H), 4.38 (s, 1H), 4.33 (bs, 1H), 4.25-4.16 (m, 2H), 4.10-4.03 (m, 1H), 3.22-3.14 (m, 3H), 3.04-2.87 (m, 4H), 2.79-2.71 (m, 1H), 2.58-2.48 (m, 1H), 2.44-2.33 (m, 1H), 2.31-2.22 (m, 1H), 2.04-1.92 (m, 1H), 1.86-1.43 (m, 11H), 1.33-1.29 (m, 1H), 0.94-0.84 (m, 1H), -0.04- -0.12(m, 1H). LC/MS: t_R = 1.97 min, 681 $(MH)^+$.

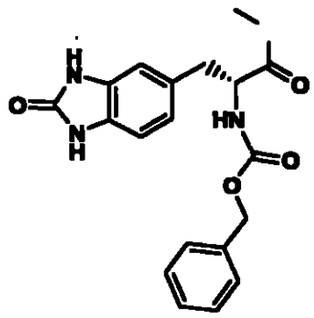
Example 232

N-((*R*)-1-(dimethylcarbamoyl)-2-(2-(trifluoromethyl)-1*H*-benzo[d]imidazol-5-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide



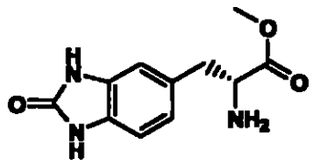
Prepared as described above for Example 231. ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.69-7.56 (m, 2H), 7.34 (d, J = 7.7 Hz, 1H), 7.17-7.08 (m, 2H), 6.92 (t, J = 7.7 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 7.7 Hz, 1H), 5.02-4.97 (m, 1H), 4.46-4.35 (m, 1H), 4.29 (s, 2H), 4.15 (d, J = 12.8 Hz, 1H), 3.26-3.11 (m, 5H), 2.87 (s, 6H), 1.86-1.68 (m, 2H), 1.66-1.59 (m, 2H). LC/MS: t_R = 2.37 min, 558 $(MH)^+$.

Benzyl (*R*)-1-(methoxycarbonyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethylcarbamate



To a dilute solution of (*R*)-2-benzyloxycarbonylamino-3-(3,4-diamino-phenyl)-propionic acid methyl ester (600 mg, 1.44 mmol) in tetrahydrofuran (125 mL) was added triethylamine (320 mg, 3.17 mmol) followed by 1,1'-carbonyldiimidazole (280 mg, 1.73 mmol). The reaction mixture was stirred at room temperature for 16 h and then filtered to remove solid. The filtrate was evaporated and subjected to flash column chromatography (1:12 methanol/methylene chloride) to give the title compound (313 mg, 59% yield). ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.28-7.21 (m, 5H), 6.94-6.83 (m, 3H), 5.06-4.95 (m, 2H), 4.46-4.41 (m, 1H), 3.68 (s, 3H), 3.17-3.11 (m, 1H), 2.95-2.88 (m, 1H). LC/MS: t_R = 2.11 min, 370 $(MH)^+$.

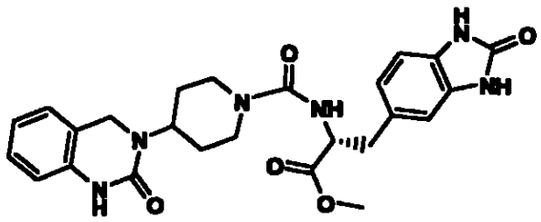
(*R*)-methyl 2-amino-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate



Benzyl (*R*)-1-(methoxycarbonyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethylcarbamate (265 mg, 0.72 mmol) and 10% palladium on carbon (30 mg) in methanol (15 mL) were agitated for 1.5 h under 50 psi hydrogen using a Parr apparatus. The reaction mixture was purged with 3 vacuum/nitrogen purge cycles. The reaction mixture was then filtered through a pad of Celite® and the pad was rinsed with several portions of methanol. The methanol filtrate was evaporated to give the title compound (168 mg, quantitative yield). ^{1}H-NMR (CD_3OD, 300 MHz) δ 6.97 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 3.71-3.64 (m, 1H), 3.67 (s, 3H), 3.04-2.89 (m, 2H). LC/MS: t_R = 0.87 min, 236 $(MH)^+$.

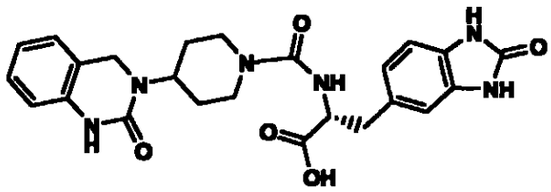
Example 233

(*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate



Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.16-7.08 (m, 2H), 6.98-6.90 (m, 4H), 6.76 (d, J = 8.1 Hz, 1H), 4.52-4.47 (m, 1H), 4.39-4.35 (m, 1H), 4.27 (s, 2H), 4.13-4.05 (m, 2H), 3.70 (s, 3H), 3.21-3.14 (m, 1H), 3.04-2.96 (m, 1H), 2.89-2.74 (m, 2H), 1.78-1.59 (m, 4H). LC/MS: t_R = 1.77 min, 493 $(MH)^+$.

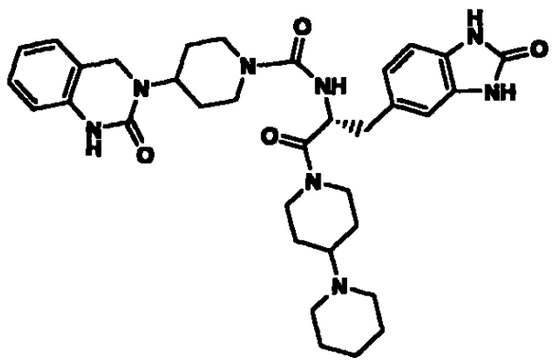
(*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoic acid



Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.16-7.09 (m, 2H), 6.99-6.90 (m, 4H), 6.76 (d, J = 7.3 Hz, 1H), 4.53-4.48 (m, 1H), 4.28 (s, 2H), 4.13-4.03 (m, 2H), 3.07-2.97 (m, 1H), 2.89-2.77 (m, 2H), 1.79-1.60 (m, 4H), 1.28-1.21 (m, 1H). LC/MS: t_R = 1.83 min, 479 $(MH)^+$.

Example 234

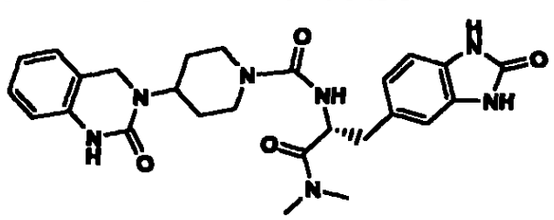
N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide



Prepared as described above for Example 231. ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.17-7.10 (m, 2H), 7.01 (s, 1H), 6.95-6.90 (m, 3H), 6.78 (d, J = 8.1 Hz, 1H), 4.98-4.93 (m, 1H), 4.62-4.55 (m, 1H), 4.41-4.33 (m, 2H), 4.20-4.16 (m, 2H), 4.04-3.96 (m, 1H), 3.05-2.85 (m, 7H), 2.71-2.57 (m, 1H), 2.53-2.32 (m, 1H), 1.86-1.76 (m, 2H), 1.70-1.61 (m, 8H), 1.50-1.41 (m, 2H), 1.03-0.89 (m, 1H), 0.10- - 0.02 (m, 1H). Mass spec.: 629.22 $(MH)^+$.

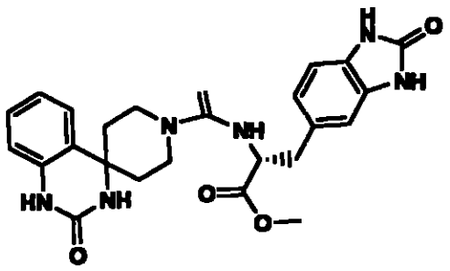
Example 235

N-((*R*)-1-(dimethylcarbamoyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide



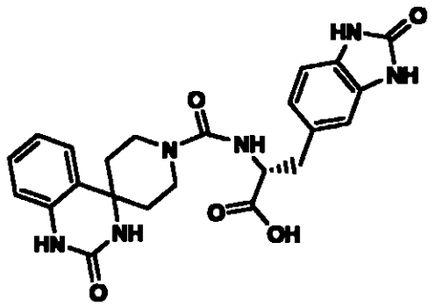
Prepared as described above for Example 231. LC/MS: t_R = 1.96 min, 506 $(MH)^+$.

(*R*)-Methyl 2-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-(1*H*)-quinazoline)carbonylamino]-3-2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate



Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. ^{1}H-NMR (DMSO-d6, 500 MHz) δ 10.54 (s, 1H), 10.50 (s, 1H), 9.22 (s, 1H), 7.21 (s, 1H), 7.13-7.10 (m, 1H), 6.96-6.79 (m, 7H), 4.29-4.25 (m, 1H), 3.82-3.78 (m, 2H), 3.60 (s, 3H), 3.32-3.23 (m, 1H), 3.16-3.14 (m, 1H), 3.00-2.90 (m, 2H), 2.08 (s, 1H), 1.67-1.55 (m, 4H). LC/MS: t_R = 1.62 min, 479 $(MH)^+$.

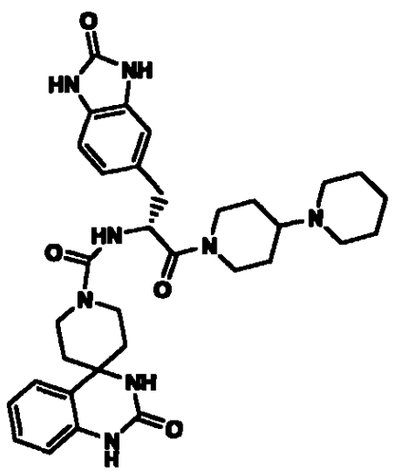
(*R*)-2-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-(1*H*)-quinazoline)carbonylamino]-3-2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoic acid



Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.19-7.14 (m, 1H), 7.05-6.95 (m, 5H), 6.81 (d, J = 7.7 Hz, 1H), 5.04-4.90 (m, 1H), 4.57-4.52 (m, 1H), 3.96-3.84 (m, 2H), 3.24-3.14 (m, 2H), 3.07-2.95 (m, 1H), 1.94-1.73 (m, 4H). LC/MS: t_R = 1.67 min, 465 $(MH)^+$.

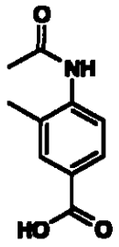
Example 236

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(2',3'-dihydro-2'-oxospiro(piperidine-4,4'-(1*H*)-quinazoline)carboxamide



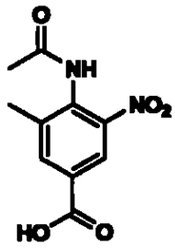
Prepared as described above for Example 231. LC/MS: t_R = 1.55 min, 615 $(MH)^+$.

4-Acetamido-3-methylbenzoic acid



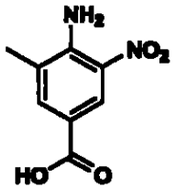
To a suspension of 4-amino-3-methylbenzoic acid (60 g, 0.40 mol) in methylene chloride (800 mL) was added triethylamine (121 g, 1.19 mol). The solution became clear. Then, acetic anhydride (81 g, 0.79 mol) was added and the reaction mixture was stirred for 60 h at room temperature. The solvent was evaporated. The residue was diluted with water (400 mL) and extracted with ethyl acetate (3 × 600 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to give the title compound as a tan solid (43 g, 56% yield). ^{1}H-NMR (d_6-DMSO, 300 MHz) δ 9.36 (s, 1H), 7.77 (s, 1H), 7.10 (s, 2H), 2.27 (s, 3H), 2.10 (s, 3H). LC/MS: t_R = 1.22 min, 194 $(MH)^+$.

4-Acetamido-3-methyl-5-nitrobenzoic acid



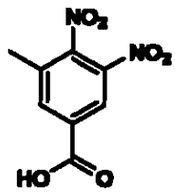
To a solution of 60% nitric acid in sulfuric acid (410 mL) was added 4-acetamido-3-methylbenzoic acid (43 g, 0.22 mol) in small portions over 40 min while cooling with an ice bath. After addition of all amide was complete, the reaction mixture was stirred for 1 h at 0°C and then very slowly poured over 1500 mL of ice. The yellow solid was collected by filtration and washed with ice cold water to give the title compound (38 g, 72% yield). ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 2.39 (s, 3H), 2.16 (s, 3H). Mass spec.: 237 $(MH)^+$.

4-Amino-3-methyl-5-nitrobenzoic acid



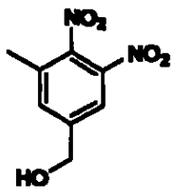
A suspension of 4-acetamido-3-methyl-5-nitrobenzoic acid (38 g, 0.16 mol) in 3N hydrochloric acid (800 mL) was heated at reflux for 8 h and then stirred at room temperature for 8 h. The yellow solid was collected by filtration and transferred to a 2 L flask with a mixture of methylene chloride and methanol. The solvent was evaporated under high vacuum to give the title compound (23 g, 74% yield). ^{1}H-NMR (DMSO-d6, 300 MHz) δ 12.79 (bs, 1H), 8.46 (s, 1H), 7.79 (s, 1H), 7.61 (s, 2H), 2.34 (s, 3H). ^{13}C-NMR (d_6-DMSO, 75 MHz) δ 166.0, 147.0, 135.1, 130.0, 126.4, 125.9, 116.7, 17.9. LC/MS: t_R = 1.23 min, 195 $(MH)^-$.

3-Methyl-4,5-dinitrobenzoic acid



To a suspension of 4-amino-3-methyl-5-nitrobenzoic acid (5.0 g, 25.5 mmol) in trifluoroacetic acid (200 mL) was added hydrogen peroxide (50 wt-% , 15 mL). The reaction mixture was heated at 50°C for 2 h and the solution eventually went from a dark orange clear solution to a pale yellow clear solution. The reaction mixture was slowly poured into ice water (800 mL). The solid was collected by filtration and dried under vacuum to give the title compound as an off-white solid (4.0 g, 70% yield). ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.59 (s, 1H), 8.40 (s, 1H), 2.45 (s, 3H). ^{13}C-NMR (CD_3OD, 75 MHz) δ 165.8, 147.4, 142.0, 139.3, 134.8, 134.6, 125.4, 17.2. Mass spec.: 225.14 $(MH)^-$.

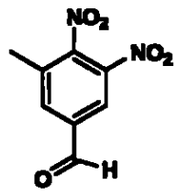
(3-Methyl-4,5-dinitrophenyl)methanol



A solution of 3-methyl-4,5-dinitrobenzoic acid (4.0 g, 17.7 mmol) in tetrahydrofuran (200 mL) was cooled to -70°C with a dry ice/acetone bath. To this solution was added borane-tetrahydrofuran (1M in tetrahydrofuran, 35.4 mL). The reaction

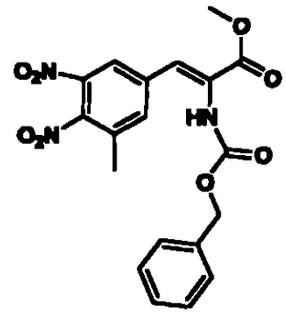
mixture was allowed to slowly warm to room temperature and was stirred for 16 h. The reaction was incomplete, was again cooled to -50°C and additional borane-tetrahydrofuran (1M in tetrahydrofuran, 35.4 mL) was added. Again, the reaction mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched with a mixture of acetic acid and water (1:1, 30 mL) while cooling at 0°C. After stirring for 30 min, all organic solvent was evaporated and the aqueous material was neutralized by pouring into ice cold saturated sodium bicarbonate (350 mL) in small portions. The aqueous layer was extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate, filtered and evaporated. The residue was subjected to flash column chromatography (1:2 hexanes/ethyl acetate) to give the title compound (3.2 g, 86% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.00(s, 1H), 7.62 (s, 1H), 4.82 (s, 2H), 2.41 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 144.5, 143.3, 140.9, 134.3, 132.9, 120.8, 63.0, 17.4.

3-Methyl-4,5-dinitrobenzaldehyde



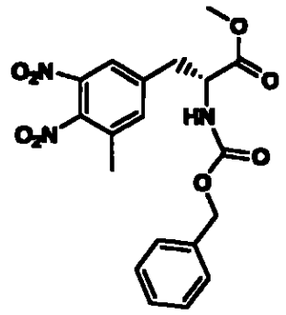
In a flame-dried flask, manganese (IV) oxide (36.0 g, 414 mmol) was azeotropically dried with toluene. Then, a solution of (3-methyl-4,5-dinitrophenyl)methanol (3.2 g, 15 mmol) in chloroform (100 mL) was transferred to the flask containing the manganese dioxide. The reaction mixture was heated at 50°C with stirring for 3 h. Upon completion of the reaction, the reaction mixture was filtered through a pad of Celite® to remove manganese dioxide and the Celite was washed with chloroform several time. The filtrate was evaporated to give the title compound (1.4 g, 44% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 10.09 (s, 1H), 8.51 (s, 1H), 8.16 (s, 1H), 2.51 (s, 3H).

Benzyl (Z)-1-(methoxycarbonyl)-2-(3-methyl-4,5-dinitrophenyl)vinylcarbamate



To a solution of *N*-(benzyloxycarbonyl)-α-phophonoglycine trimethyl ester (2.4 g, 7.3 mmol) in tetrahydrofuran (40 mL) at -78°C was added 1,1,3,3-tetramethylguanidine (729 mg, 6.33 mmol) and the mixture was stirred for 1 h at -78°C. To this mixture was added a solution of 3-methyl-4,5-dinitrobenzaldehyde (1.4 g, 6.7 mmol) in tetrahydrofuran (15 mL). The reaction mixture was allowed to slowly warm to room temperature and was then stirred for 16 h at room temperature. The solvent was evaporated and the residue subjected to flash column chromatography (gradient, 1:2 to 1:1 ethyl acetate/hexanes). The product was then recrystallized from ethyl acetate/hexanes (1:1) to give the title compound (1.7 g, 62% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.55 (s, 1H), 7.33-7.22 (m, 6H), 6.94 (bs, 1H), 5.06 (s, 2H), 3.89 (s, 3H), 2.29 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 164.7, 152.5, 143.1, 140.6, 137.7, 137.0, 135.3, 132.5, 128.8, 128.7, 128.6, 127.1, 123.5, 123.2, 68.3, 53.5, 17.4. Mass spec.: 414.20 $(MH)^-$.

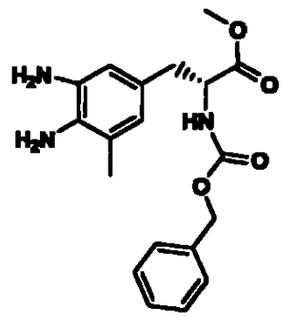
Benzyl (*R*)-1-(methoxycarbonyl)-2-(3-methyl-4,5-dinitrophenyl)ethylcarbamate



In a glove bag that was subjected to 3 vacuum/nitrogen purge cycles, an AIRFREE® (Schlenk) reaction flask equipped with stir bar was charged with (-)-1,2-bis((2R,5R)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium (I) trifluoromethylsulfonate (125 g, 0.173 mmol, 4 mol%), sealed with a rubber septum,

and removed from the glove bag. The benzyl (Z)-1-(methoxycarbonyl)-2-(3-methyl-4,5-dinitrophenyl)vinylcarbamate (1.65 g, 3.97 mmol) was weighed into a second AIRFREE® (Schlenk) reaction flask equipped with stir bar and sealed with a rubber septum. After 3 vacuum/nitrogen purge cycles, it was dissolved in a mixture of anhydrous methylene chloride (40 mL). The solvent was deoxygenated prior to addition by sparging with nitrogen for at least 1 h. Once in solution, the mixture was again subjected to 3 vacuum/nitrogen purge cycles. The dehydroamino acid solution was introduced into the AIRFREE® (Schlenk) reaction flask containing the catalyst via cannula. The reaction mixture was subjected to 5 vacuum/hyrogen purge cycles before opening the flask to 1 atmosphere of hydrogen. After 16 h, the reaction mixture was purged with 3 vacuum/nitrogen purge cycles. The solvent was evaporated and the residue was subjected to column chromatography (1:1 ethyl acetate/hexanes) to give the title compound (1.58 g, 95%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.75 (s, 1H), 7.39-7.33 (m, 6H), 5.37 (d, J = 7.0 Hz, 1H), 5.15-5.04 (m, 2H), 4.70-4.46 (m, 1H), 3.77 (s, 3H), 3.30 (dd, J = 13.9, 5.5 Hz, 1H), 3.12 (dd, J = 13.9, 6.2 Hz, 1H), 2.33 (s, 3H). LC/MS: t_R = 2.71 min, 418 $(MH)^+$.

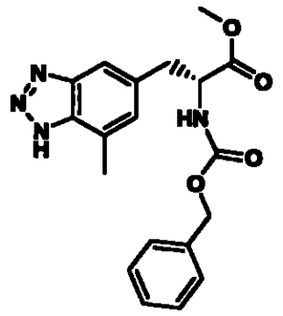
Benzyl (*R*)-1-(methoxycarbonyl)-2-(3,4-diamino-5-methylphenyl)ethylcarbamate



Solid ammonium formate (755 mg, 11.9 mmol) was added in small portions at 0°C to suspension of benzyl (*R*)-1-(methoxycarbonyl)-2-(3-methyl-4,5-dinitrophenyl)ethylcarbamate (500 mg, 1.20 mmol) and zinc powder (470 mg, 7.19 mmol) in methanol (20 mL, degassed with nitrogen for 2 h). The resulting mixture was stirred at room temperature for 60 h. Reaction was incomplete. The reaction mixture was again cooled to 0°C and additional zinc powder (470 mg, 7.19 mmol) was added. The reaction was stirred for 4 h at which time the reaction was complete. The reaction mixture was filtered to remove zinc. The filtrate was evaporated. A

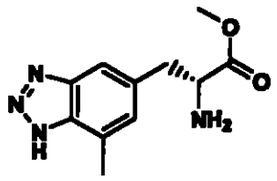
mixture of toluene and ethyl acetate (1:1) were added, followed by acetic acid (2 mL). The mixture was further diluted until all organic solids dissolved, then it was washed with water, brine, dried over sodium sulfate, and evaporated. The residue was then redissolved in ethyl acetate and 4N hydrogen chloride in dioxane (4 mL) was added. The solvent was evaporated to give the title compound as the dihydrochloride salt (515 mg, quantitative yield). ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.35-7.30 (m, 5H), 6.94-6.93 (m, 2H), 5.03 (s, 2H), 4.42-4.37 (m, 1H), 3.70 (s, 3H), 3.09-3.03 (m, 1H), 2.87-2.79 (m, 1H), 2.25 (s, 3H). LC/MS: t_R = 1.79 min, 358 $(MH)^+$.

Benzyl (*R*)-1-(methoxycarbonyl)-2-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)ethylcarbamate



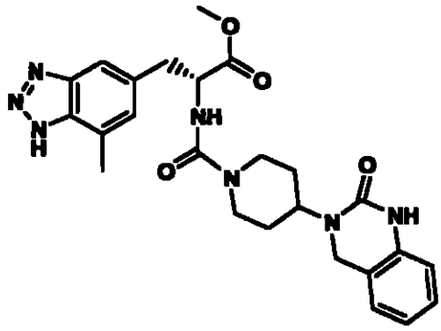
To a solution of benzyl (*R*)-1-(methoxycarbonyl)-2-(3,4-diamino-5-methylphenyl)ethylcarbamate (250 mg, 0.58 mmol) in acetic acid (6 mL) and water (10 mL) was added a solution of sodium nitrite (40 mg, 0.58 mmol) in water (1 mL), dropwise over several minutes at room temperature. The resulting mixture was stirred at room temperature for 30 min, then cooled to 0°C. A mixture of ammonium hydroxide and water (1:1, 15 mL) was added to adjust pH to 11. The mixture was extracted with ethyl acetate twice. The organic layers washed with brine and dried over sodium sulfate. After filtration, solvents were removed *in vacuo* and the residue was purified by flash column chromatography (1:1 ethyl acetate/hexanes) on silica gel to afford the title compound as a tan solid (155 mg, 72% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 1H), 7.32-7.28 (m, 6H), 6.93 (s, 1H), 5.40 (d, J = 8.1 Hz, 1H), 5.13-5.02 (m, 2H), 4.76-4.69 (m, 1H), 3.73 (s, 3H), 3.28 (dd, J = 13.9, 5.5 Hz, 1H), 3.16 (dd, J = 13.9, 6.2 Hz, 1H), 2.64 (s, 3H). LC/MS: t_R = 2.30 min, 369 $(MH)^+$.

(*R*)-Methyl 2-amino-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)propanoate



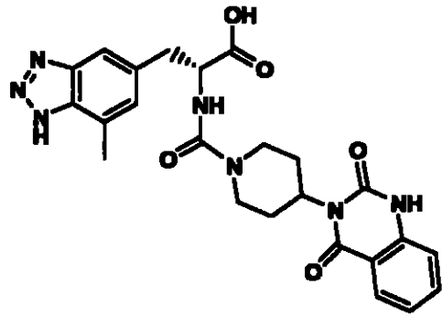
Benzyl (*R*)-1-(methoxycarbonyl)-2-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)ethylcarbamate (146 mg, 0.40 mmol) was dissolved in 12 mL of a solution of 4.4% formic acid in methanol. The reaction flask containing this solution was equipped with a magnetic stirbar and then flushed with nitrogen over several minutes. To the solution was added palladium on carbon (10%, 200 mg) and the reaction was stirred for 16 h at room temperature under nitrogen atmosphere. The reaction mixture was filtered through a pad of Celite® washing the pad several times with methanol. The filtrate was evaporated to give the title compound (quantitative yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.40 (bs, 1H), 7.55 (s, 1H), 7.14 (s, 1H), 4.29-4.24 (m, 1H), 3.78 (s, 3H), 3.39-3.19 (m, 2H), 2.69 (s, 3H). LC/MS: t_R = 1.18 min, 235 $(MH)^+$.

(*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)propanoate



Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. LC/MS: t_R = 2.17 min, 492 $(MH)^+$.

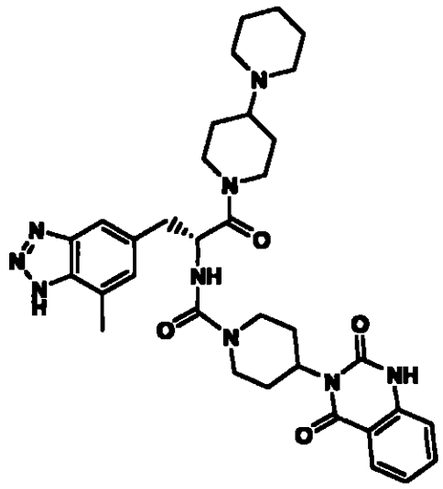
(*R*)-2-(4-(1,2-dihydro-2,4-dioxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)propanoic acid



Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. LC/MS: t_R = 2.11 min, 492 $(MH)^+$.

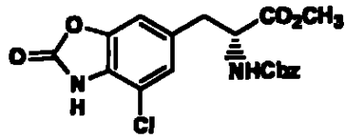
Example 237

4-(1,2-dihydro-2,4-dioxoquinazolin-3(4*H*)-yl)-*N*-((*R*)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide



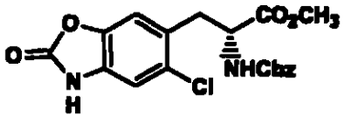
Prepared as described above for Example 231. ^{1}H-NMR (CD_3OD, 300 MHz) δ 8.01 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.28-7.11 (m, 4H), 5.06-5.00 (m, 1H), 4.70-4.60 (m, 1H), 4.31-4.17 (m, 2H), 3.50-3.44 (m, 1H), 3.20-2.82 (m, 7H), 2.75-2.47 (m, 6H), 2.12-2.02 (m, 2H), 1.93-1.67 (m, 11H), 1.37-1.28 (m, 2H, 0.97-0.79 (m, 2H), 0.23-0.09 (m, 1H). Mass spec.: 642 $(MH)^+$.

(R)-2-Benzyloxycarbonylamino-3-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



A mixture of (*R*)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (373 mg, 1.01 mmol), N-chlorosuccinimide (168 mg, 1.26 mmol), silica gel (EM Scientific, 230 – 400 mesh, 3.73 g) in dichloroethane (20 mL) was heated at 90°C for 16 h. After cooling down to room temperature, the solvents were removed in vacuo. The residue was subjected to silica gel chromatography using ethyl acetate/hexanes (1:2) as eluent to afford the title compound (40 mg, 9.8%), also 2-benzyloxycarbonylamino-3-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (78 mg, 19%). The structure was confirmed by 2D NMR and by comparison with that of 2-benzyloxycarbonylamino-3-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester prepared by the reaction shown below. ^{1}H-NMR (CD_3COCD_3, 500 MHz) δ 7.37 – 7.27 (m, 5H), 7.18 (d, J = 1.0 Hz, 1H), 7.16 (s, 1H), 6.76 (d, J = 8.5 hz, 1H), 5.06 (d, J = 12.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.55 – 4.51 (m, 1H), 3.72 (s, 3H), 3.26 (dd, J = 14.0, 5.0 Hz, 1H), 3.04 (dd, J = 14.0, 9.5 Hz, 1H); ^{13}C-NMR (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 154.0, 144.8, 137.6, 133.3, 128.7, 128.2, 128.0, 127.9, 125.0, 66.3, 55.9, 52.0, 37.3; Mass spec. 405 (MH^+).

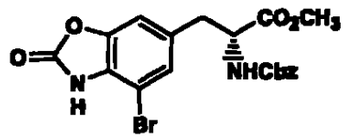
(R)-2-Benzyloxycarbonylamino-3-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



N-Chlorosuccinimide (315 mg, 2.36 mmol) was added to a solution of (*R*)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (700 mg, 1.89 mmol) in acetic acid (50 mL) at room temperature. The mixture was heated at 100°C for 16h. After it was cooled down to room temperature, solvents were removed in vacuo. The residue was subjected to silica gel chromatography using ethyl acetate/hexanes (4:6) then (1:1) as eluent to afford the

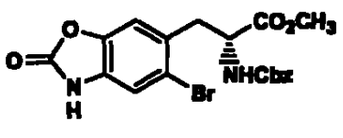
title compound as an off-yellow solid (242 mg, 32%). The structure of the product was confirmed by 2D NMR. ^{1}H-NMR (CD_3COCD_3, 500 MHz) δ 10.47 (s, 1H), 7.36 – 7.28 (m, 6H), 7.20 (s, 1H), 6.80 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.65 - 4.60 (m, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.0, 5.0 Hz, 1H), 3.08 (dd, J = 14.0, 10.5 Hz, 1H); ^{13}C-NMR (CD_3COCD_3, 125 MHz) δ 172.2, 156.5, 154.5, 143.1, 137.5, 130.8, 129.0, 128.9, 128.7, 128.2, 128.0, 112.8, 110.9, 66.3, 54.3, 52.1, 35.8; Mass spec. 405 (MH^+).

(R)-2-Benzyloxycarbonylamino-3-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



A mixture of (*R*)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (418 mg, 1.13 mmol), N-bromosuccinimide (221 mg, 1.24 mmol), silica gel (EM Scientific, 230 – 400 mesh, 2.51 g) and methylene chloride (70 mL) was stirred at room temperature for 16 h. Solvents were removed in vacuo and the residue was subjected to silica gel chromatography using ethyl acetate/hexanes (2:3) as eluent to afford the title compound. ^{1}H-NMR (CD_3COCD_3, 500 MHz) δ 10.71 (s, 1H), 7.35 – 7.28 (m, 6H), 7.21 (s, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.06 (d, 12.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.56 – 4.51 (m, 1H), 3.73 (s, 3H), 3.26 (dd, J = 14.0, 5.0 Hz, 1H), 3.03 (dd, J = 14.0, 10.0 Hz, 1H); ^{13}C-NMR (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 153.8, 144.4, 137.6, 133.7, 129.8, 128.7, 128.2, 128.0, 127.8, 110.1, 100.9, 66.3, 55.9, 52.0, 37.3; Mass spec. 448.03 (MH^+).

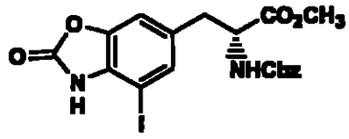
(R)-2-Benzyloxycarbonylamino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



A mixture of (*R*)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (1.07 g, 2.89 mmol), N-bromosuccinimide (643 mg, 3.61 mmol), and acetic acid (150 mL) was heated at 105°C for 14 h. After cooling to

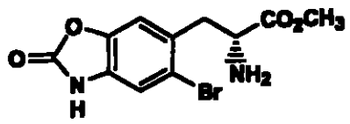
room temperature, the solvents were removed in vacuo. The residue was subjected to silica gel chromatography using ethyl acetate/hexanes (2:3), then (1:1) as eluent to afford the title compound (446 mg, 34%). The structure of the title compound was confirmed by 2D NMR. ^{1}H-NMR (CD_3COCD_3, 500 MHz) δ 10.46 (s, 1H), 7.36 – 7.28 (m, 7H), 6.82 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.67 – 4.62 (m, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.0, 5.0 Hz, 1H), 3.10 (dd, J = 14.0, 10.5 Hz, 1H); ^{13}C-NMR (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 154.2, 143.7, 137.6, 131.1, 130.6, 128.7, 128.2, 128.0, 118.2, 113.9, 112.9, 66.2, 54.3, 52.1, 38.3; Mass spec. 448.03 (MH^+).

(R)-2-Benzyloxycarbonylamino-3-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



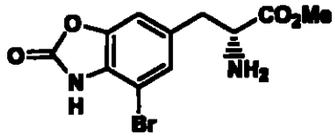
A mixture of (*R*)-2-benzyloxycarbonylamino-3-(2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (324 mg, 0.87 mmol), $I(PyH)_2BF_4$ (409 mg, 1.08 mmol), silica gel (EM Scientific, 230 – 400 mesh, 3.24 g) and dichloroethane (20 mL) was heated at 90°C for 6 h. After cooling to room temperature the solvents were removed in vacuo. The residue was subjected to silica gel chromatography using ethyl acetate/hexanes (1:2) as eluent to afford the title compound (175 mg, 40%). The structure of the title compound was confirmed by 2D NMR. ^{1}H-NMR (CD_3COCD_3, 500 MHz) δ 10.47 (s, 1H), 7.46 (s, 1H), 7.37 – 7.29 (m, 5H), 7.22 (s, 1H), 6.74 (d, J = 8.5 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.54 – 4.49 (m, 1H), 3.72 (s, 3H), 3.23 (dd, J = 14.0, 5.0 Hz, 1H), 3.01 (dd, J = 14.0, 9.5 Hz, 1H); ^{13}C-NMR (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 153.4, 143.3, 137.6, 134.1, 133.64, 133.60, 128.7, 128.2, 128.0, 110.7, 71.1, 66.3, 56.0, 52.0, 37.1; Mass spec. 496.01 (MH^+).

(*R*)-2-Amino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



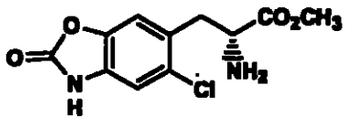
Trimethylsilyliodide (73 mL, 0.73 mmol) was added to a solution of azotropically dried (*R*)-2-benzyloxycarbonylamino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester (146 mg, 0.33 mmol) in acetonitrile (10 mL) at room temperature, and the resulting mixture was stirred at room temperature for 2 h. Triethylamine (0.12 mL) was added and the mixture was stirred at room temperature for 15 min. The solvents were removed in vacuo, and the residue was extracted with ethyl acetate. The combined organics were washed with sodium bicarbonate and brine, dried over sodium sulfate and filtered. Solvents were removed and the residue was used directly in the next step. Mass spec. 315.10 $(MH)^+$.

(*R*)-2-Amino-3-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



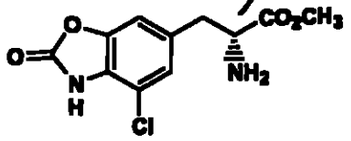
Prepared as described above for (*R*)-2-amino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. Mass spec. 315.06 $(MH)^+$.

(*R*)-2-Amino-3-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



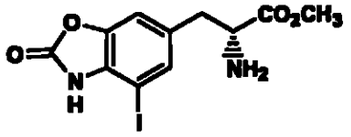
Prepared as described above for (*R*)-2-amino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. Mass spec. 271.10 $(MH)^+$.

(*R*)-2-Amino-3-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester



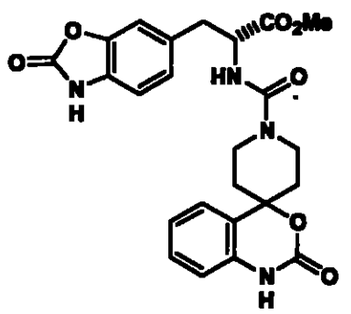
Prepared as described above for (*R*)-2-amino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. Mass spec. 271.16 $(MH)^+$.

(*R*)-2-Amino-3-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester:



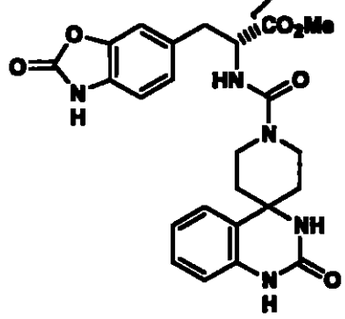
Prepared as described above for (*R*)-2-Amino-3-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-propionic acid methyl ester. Mass spec. 363.04 $(MH)^+$.

(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carbonyl]-amino}-propionic acid methyl ester



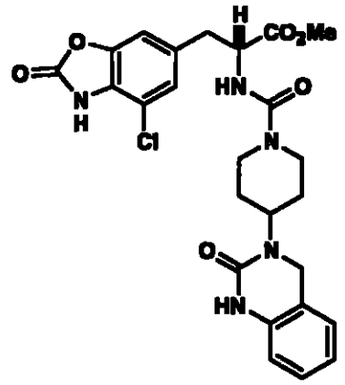
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 481.20 $(MH)^+$.

(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carbonyl]-amino}-propionic acid methyl ester



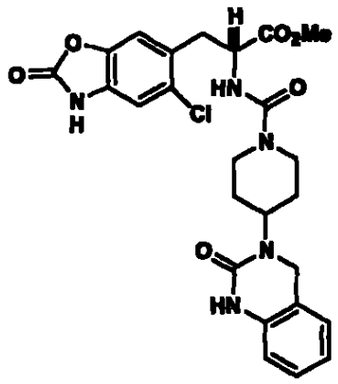
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 480.24 $(MH)^+$.

(*R*)-3-(4-Chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



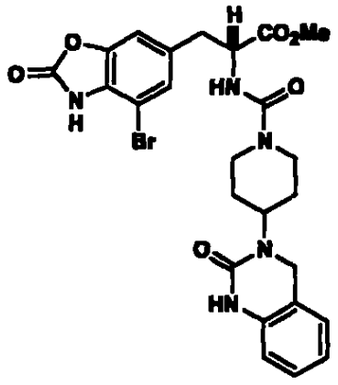
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 528.16 $(MH)^+$.

(*R*)-3-(5-Chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



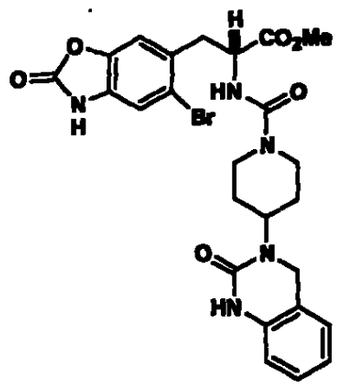
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 528.20 $(MH)^+$.

(*R*)-3-(4-Bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



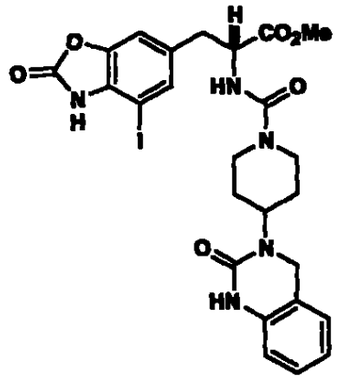
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 572.20 $(MH)^+$.

(*R*)-3-(5-Bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



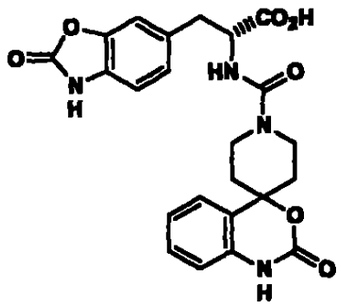
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 572.15 $(MH)^+$.

(*R*)-3-(4-Iodo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester



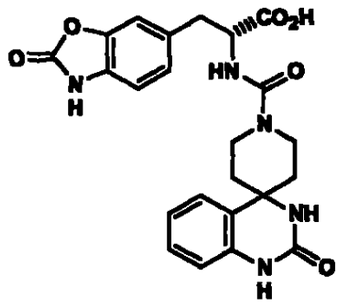
Prepared as described above for (*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoate. Mass spec. 620.20 $(MH)^+$.

(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carbonyl]-amino}-propionic acid



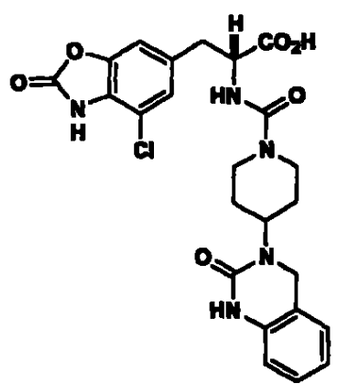
Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 467.18 $(MH)^+$.

(R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carbonyl]-amino}-propionic acid



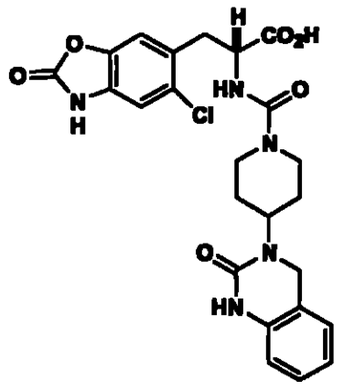
Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 466.20 $(MH)^+$.

(*R*)-3-(4-Chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



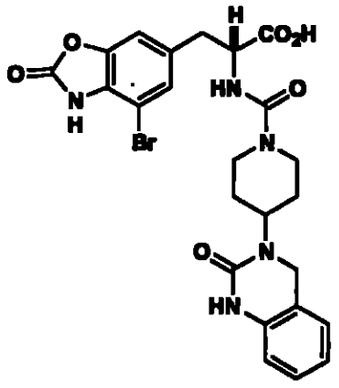
Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 514.20 $(MH)^+$.

(*R*)-3-(5-Chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



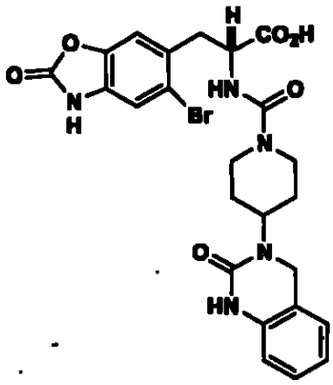
Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 514.24 $(MH)^+$.

(*R*)-3-(4-Bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



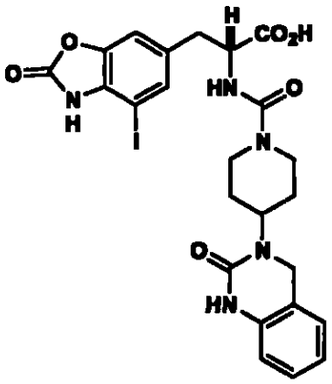
Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 558.30 $(MH)^+$.

(*R*)-3-(5-Bromo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 558.25 $(MH)^+$.

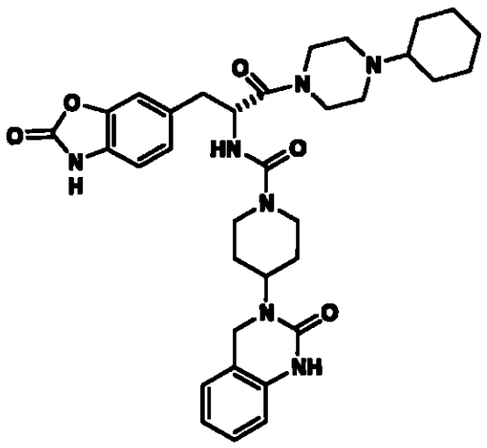
(*R*)-3-(4-Iodo-2-oxo-2,3-dihydro-benzooxazol-6-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid



Prepared as described above for (*R*)-2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)propanoic acid. Mass spec. 606.10 $(MH)^+$.

Example 238

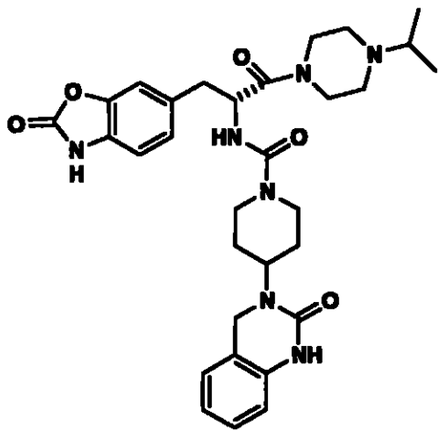
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



Prepared as described above for Example 231. LC/MS: t_R = 1.80 min, 630.37 $(MH)^+$.

Example 239

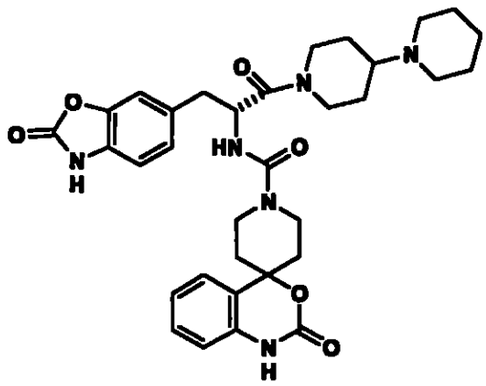
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-isopropyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



Prepared as described above for Example 231. LC/MS: t_R = 1.71 min, 590.34 $(MH)^+$.

Example 240

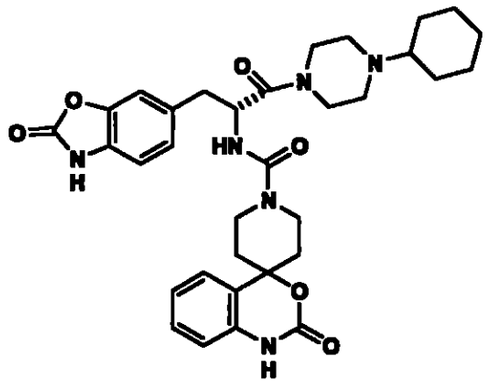
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide



Prepared as described above for Example 231. LC/MS: t_R = 1.64 min, 617.34 $(MH)^+$.

Example 241

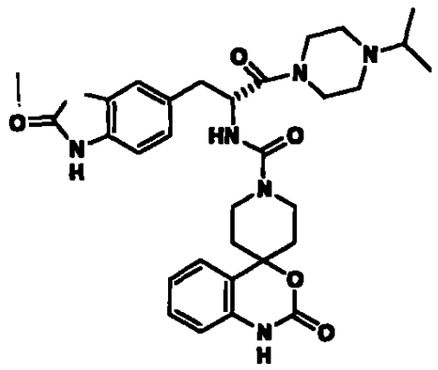
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide



Prepared as described above for Example 231. LC/MS: t_R = 1.69 min, 617.35 $(MH)^+$.

Example 242

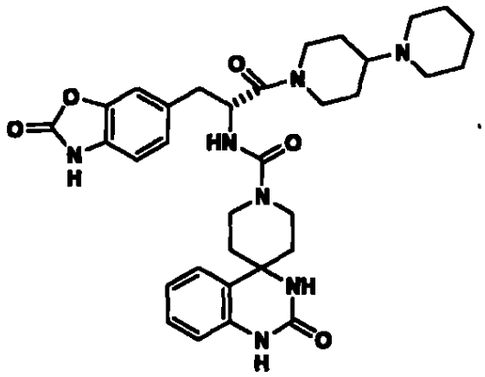
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide



Prepared as described above for Example 231. LC/MS: t_R = 1.57 min, 577.32 $(MH)^+$.

Example 243

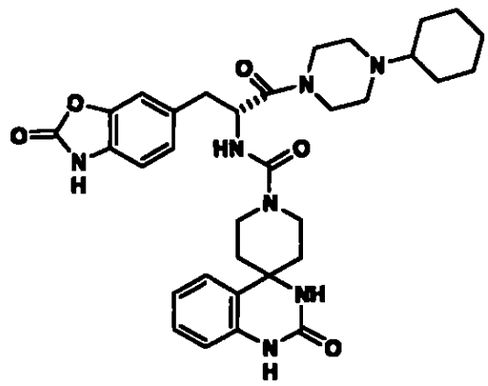
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide



Prepared as described above for Example 231. LC/MS: t_R = 1.74 min, 616.37 $(MH)^+$.

Example 244

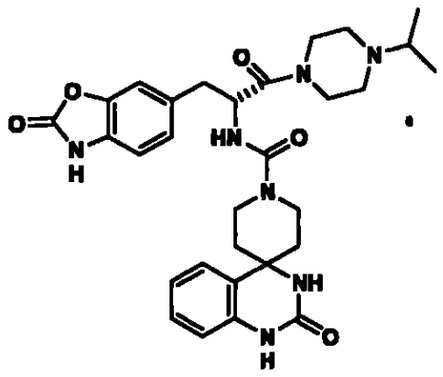
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide



Prepared as above. LC/MS: t_R = 1.79 min, 616.36 $(MH)^+$.

Example 245

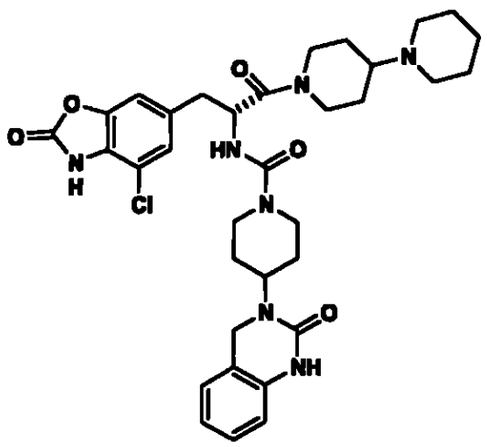
(*R*)-*N*-((R)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide



Prepared as described above for Example 231. LC/MS: t_R = 1.67 min, 576.34 $(MH)^+$.

Example 246

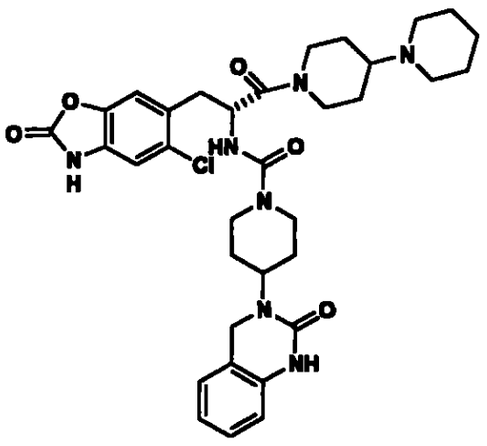
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 231. LC/MS: t_R = 1.91 min, 664.35 $(MH)^+$.

Example 247

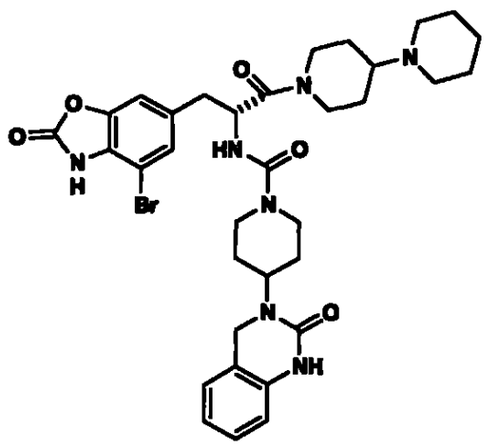
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 231. LC/MS: t_R = 1.91 min, 664.34 $(MH)^+$.

Example 248

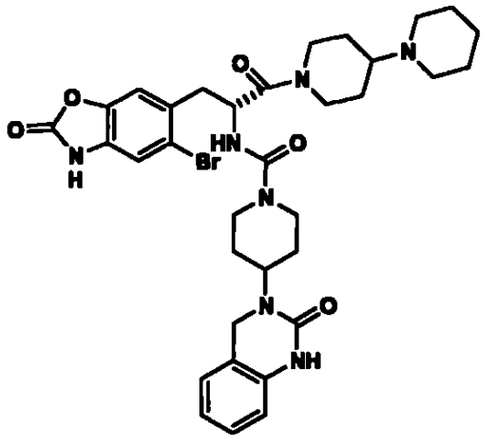
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 231. *LC/MS*: t_R = 1.96 min, 708.31 $(MH)^+$.

Example 249

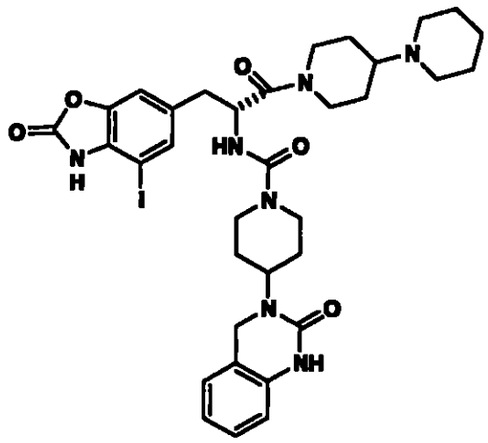
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 231. *LC/MS*: t_R = 1.96 min, 708.31 $(MH)^+$.

Example 250

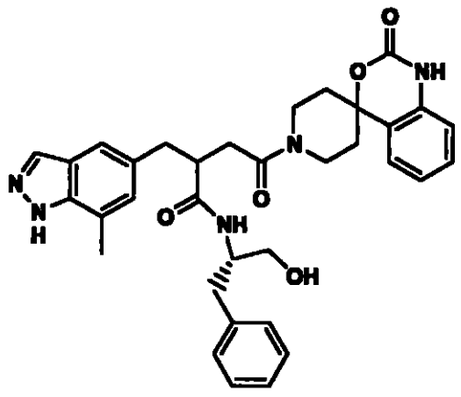
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 231. LC/MS: t_R = 1.97 min, 756.36 (MH^+).

Example 251

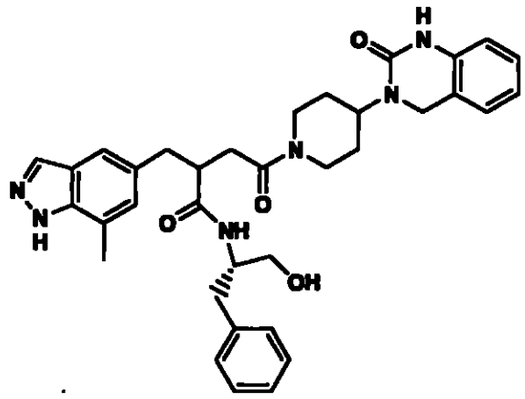
(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.38 min, 596 $(MH)^+$.

Example 252

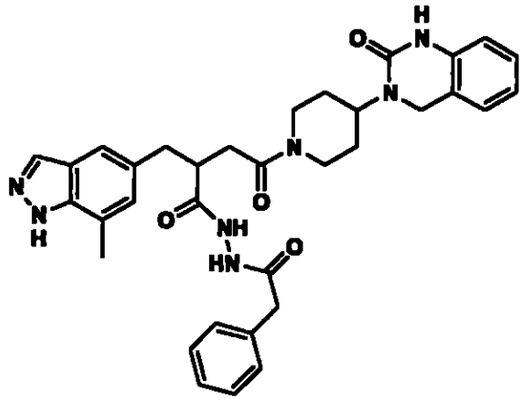
(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2 H-quinazolin-3-yl)-piperidin-1-yl]-butyramide



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.50 min, 609 $(MH)^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.90 (1H, s), 7.64-7.84 (1H, m), 6.71-7.42 (11H, m), 4.58 (1H, m), 3.82-4.50 (6H, m), 2.21-3.52 (13H, m), 1.42-1.87 (4H, m).

Example 253

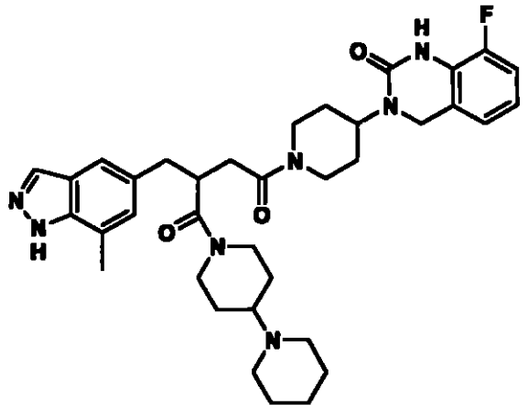
(±)-Phenyl-acetic acid N'-{2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyryl}-hydrazide



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.43 min, 630 $(M+Na)^+$.

Example 254

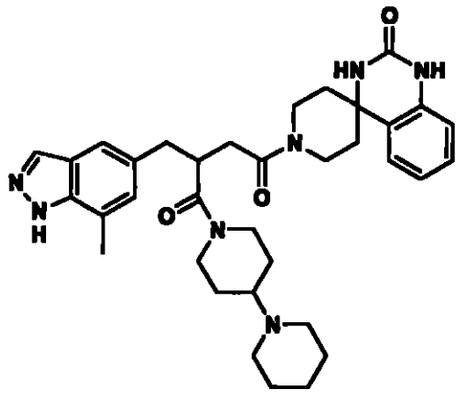
(±)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(8-fluoro-2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(7-methyl-1H-indazol-5-ylmethyl)-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.18 min, 644 $(MH)^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, s), 6.82-7.40 (6H, m), 4.48-4.70 (3H, m), 4.31 (2H, s), 3.85-4.11 (2H, m), 3.65 (1H, m), 2.70-3.16 (5H, m), 2.53 (3H, s), 0.72-2.52 (23H, m).

Example 255

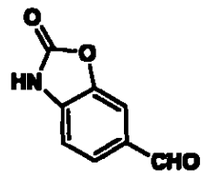
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline]-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.09 min, 612 $(MH)^+$.

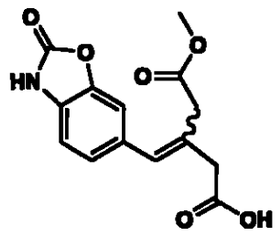
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2-Oxo-2,3-dihydro-benzooxazole-6-carbaldehyde



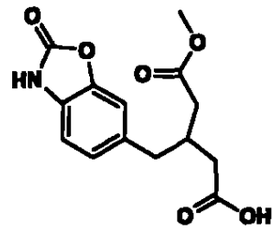
A solution of 6-bromo-3H-benzooxazol-2-one (0.9236g , 4.31 micromoles) in anhydrous tetrahydrofuran (25 mL) and dimethylformamide (3 mL) under nitrogen was cooled to –78°C before addition of n-butyllithium (2.5M in hexane) (3.8 mL, 2.2 equiv). After stirring for 10 min at –78°C, 24 mL of sec-butyllithium (1.4 M in cyclohexane, 8 equiv) was added. The reaction was stirred while slowly warming to –40°C. When this temperature was reached, the reaction was quenched by addition of methanol. The reaction mixture was concentrated in vacuo and water was added. The aqueous layer was acidified with 1N HCl (ca. pH 5) and extracted with ethyl acetate (3 x 50 mL), dried over sodium sulfate, filtered and concentrated to give the product, 0.6402 g (91%). MS (ESI) 164 $(MH)^+$. ^1H NMR (400 MHz, DMSO-d6) δ 9.90 (1H, s), 7.79 (1H, d, J=8.0 Hz), 7.74 (1H, s), 7.28 (1H, d, J=8.0 Hz).

3-(2-Oxo-2,3-dihydro-benzooxazol-6-ylmethylene)-pentanedioic acid monomethyl ester



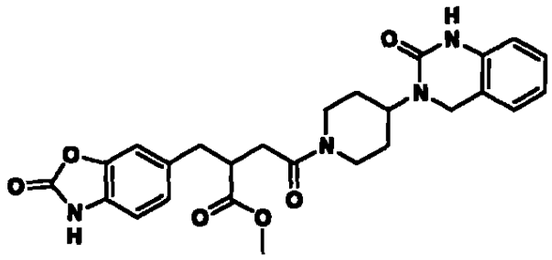
Prepared as described above for 2-(7-methyl-1H-indazol-5-ylmethylene)-succinic acid 1-methyl ester (1.4 g, 90% yield). MS (ESI) 300 $(M+Na)^+$.

(±)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-pentanedioic acid monomethyl ester



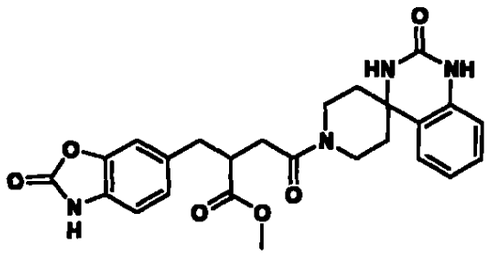
Prepared as described above for (±)-2-(7-methyl-1H-indazol-5-ylmethyl)-succinic acid 1-methyl ester (1.4 g, 99% yield). MS (ESI) 302 $(M+Na)^+$.

(±)-4-Oxo-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid methyl ester



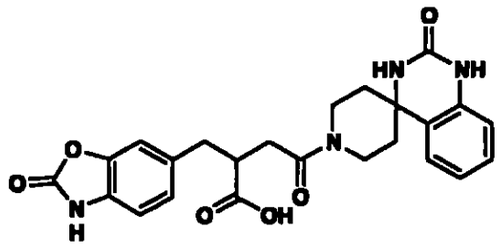
Prepared as described above for (±)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid methyl ester. MS (ESI) 493 $(MH)^+$.

(±)-4-Oxo-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butyric acid methyl ester



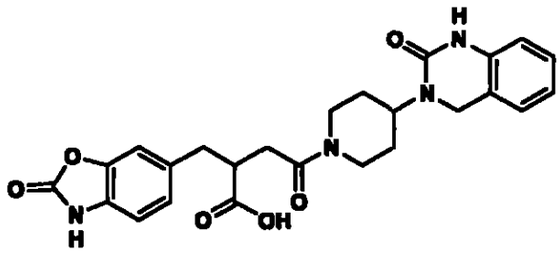
Prepared as described above for (±)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid methyl ester. MS (ESI) 479 $(MH)^+$.

(±)-4-Oxo-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butyric acid



Prepared as described above for (±)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid. MS (ESI) 465 $(MH)^+$.

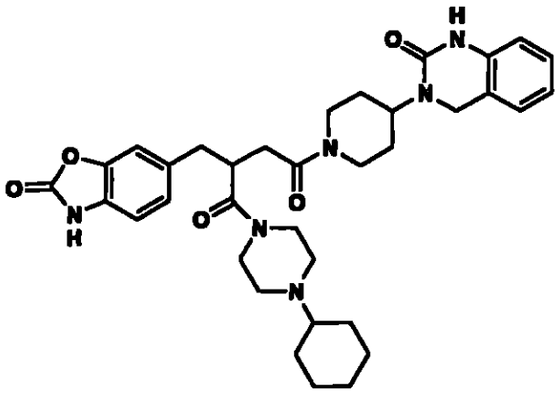
(±)-4-Oxo-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid



Prepared as described above for (±)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid. MS (ESI) 479 $(MH)^+$.

Example 256

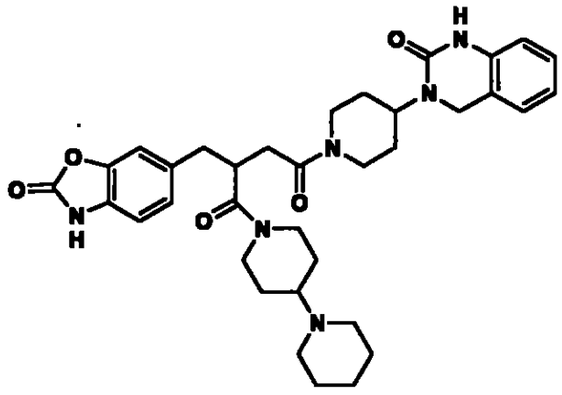
(±)-1-(4-Cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.10 min, 629 $(MH)^+$.

Example 257

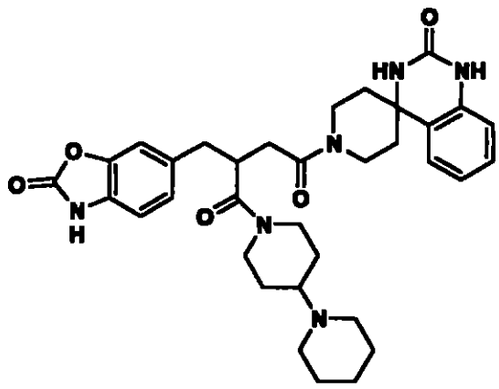
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.08 min, 629 $(MH)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (1H, s), 8.28 (1H, d, J=11.2 Hz),6.90-7.25 (5H, m), 6.75 (1H, d, J=8.0 Hz), 4.40-4.79 (3H, m), 4.35 (2H, s), 2.27-3.98 (19H ,m), 1.46-2.10 (9H, m), 1.36 (1H, m), 1.08 (1H, m), 0.12 (1H, m).

Example 258

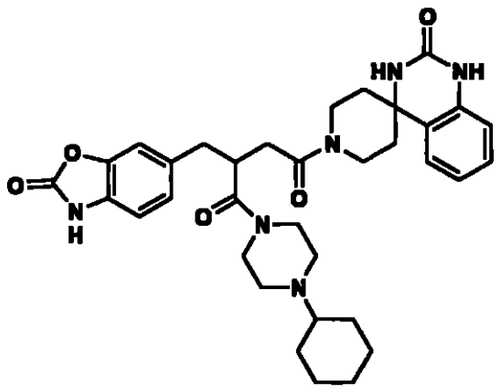
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.02 min, 615 $(MH)^+$.

Example 259

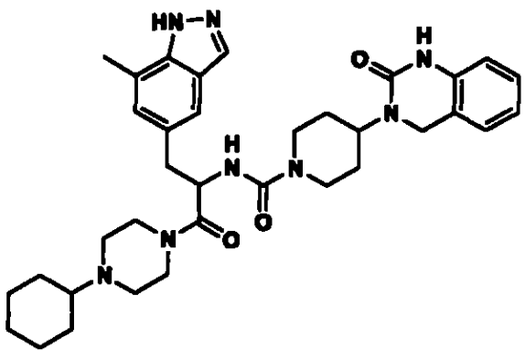
(±)-1-(4-cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione



Prepared as described above for (±)-1-[1,4']bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione. LC/MS: t_R=1.04 min, 615 $(MH)^+$.

Example 260

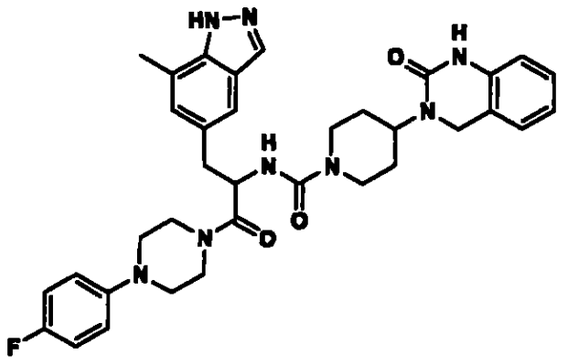
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 16. ^{1}H-NMR (CD_3OD, 500 MHz) δ 0.81 (1H, m), 0.89 (1H, m), 1.02 (1H, m), 1.1-2.0 (12H, m), 2.23 (1H, d), 2.47 (1H, d), 2.61 (3H, s), 2.90 (4H, t), 3.08 (4H, m), 3.2-3.5 (4H, m), 3.82 (1H, m), 4.14 (2H, d), 4.29 (2H, s), 4.40 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.12 (3H, m), 7.47 (1H, s), 8.01 (1H, s). Mass spec.: 627.47 $(MH)^+$.

Example 261

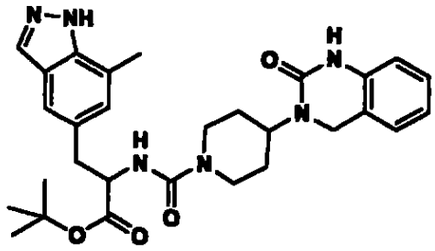
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



Prepared as described above for Example 16. LC/MS: t_R=2.34 min, 621.42 $(MH)^+$.

Example 262

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester

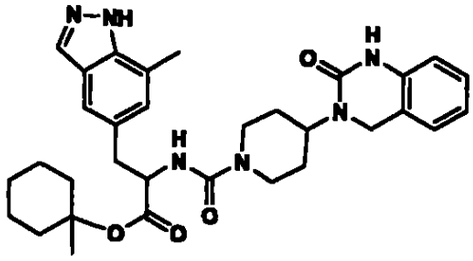


A solution of (±)-3-(7-methyl-1H-indazol-5-yl)- 2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]- amino}-propionic acid (50 mg, 0.105 mmol) and dicyclohexylcarbodiimide (25 mg, 0.12 mmol) in dimethylformamide was stirred for 30 min at room temperature, and then pentafluorophenol (26 mg, 1.3 mmol) was added. Stirring was continued at room temperature overnight, and then the solvent was removed, the residue was dried under high vacuum for 4 h. The crude pentafluorophenyl ester was used without further purification in the next step.

To a solution of tert-butyl alcohol (10 equiv.) in tetrahydrofuran at -78°C under nitrogen was added 1.4M sec-butyllithium in cyclohexane (10 equiv.). After 10-15 min, a solution of pentafluorophenol ester (1 equiv.) in tetrahydrofuran was added. The reaction mixture was stirred at room temperature overnight. The solvents were removed in vacuo, and the residue was purified by preparative-HPLC to give the desired compound. ^{1}H-NMR(CD_3OD) δ 1.40 (s, 9H) 1.56 (m, 4H), 2.54 (s, 3H) 2.85 (m, 2H) 3.05 (m, 1H) 3.19 (m, 1H) 4.14 (m, 4H) 4.44 (m, 2H) 6.76 (d, J=7.68 Hz, 1H) 6.93 (t, J=7.5 Hz, 1H) 7.10 (m, 3H) 7.14 (s, 1H) 7.97 (s, 1H). LC/MS: t_R=2.19 min, 533.36 $(MH)^+$.

Example 263

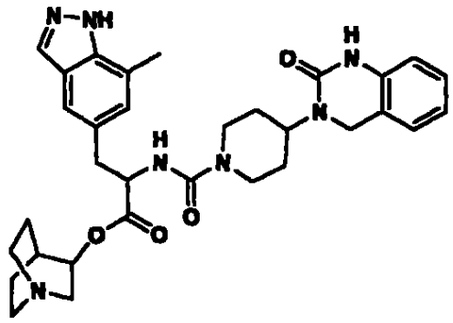
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl cyclohexyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester. LC/MS: t_R=2.47 min, 574.39 $(MH)^+$.

Example 264

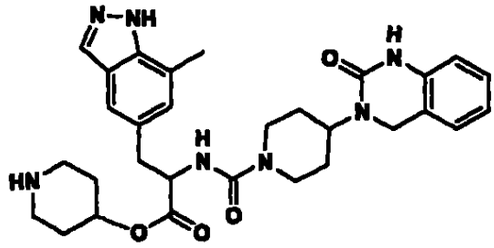
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester



To a solution of (±)-3-(7-methyl-1H-indazol-5-yl)- 2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]- amino}-propionic acid (50 mg, 0.105 mmol), EDCI (100 mg), and 4-dimethylaminopyridine (0.2 equiv.) in dimethylformamide was added aza-bicyclo[2.2.2]oct-3-yl alcohol (0.525 mmol, 5 equiv.). The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate, and purified by preparative HPLC to yield the desired compound. LC/MS: t_R=1.62 min, 586.41 $(MH)^+$.

Example 265

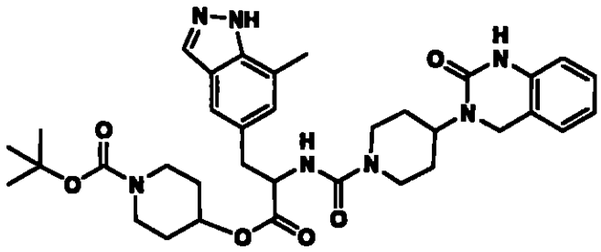
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid piperidin-4-yl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester. LC/MS: t_R=1.58 min, 560.37 $(MH)^+$.

Example 266

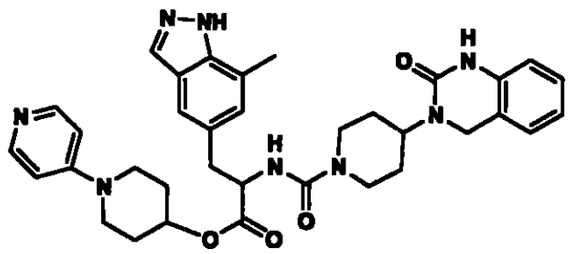
(±)-4-(3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyloxy)-piperidine-1-carboxylic acid tert-butyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester. LC/MS: t_R=2.38 min, 660.42 $(MH)^+$.

Example 267

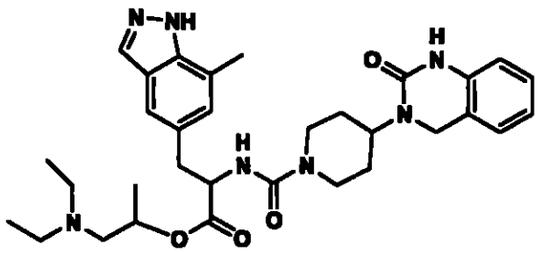
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester. LC/MS: t_R=1.67 min, 637.43 $(MH)^+$.

Example 268

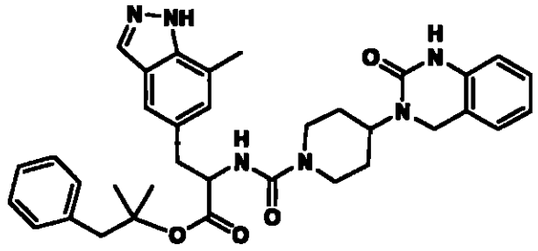
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-diethylamino-1-methyl-ethyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester. LC/MS: t_R=1.66 min, 590.44 $(MH)^+$.

Example 269

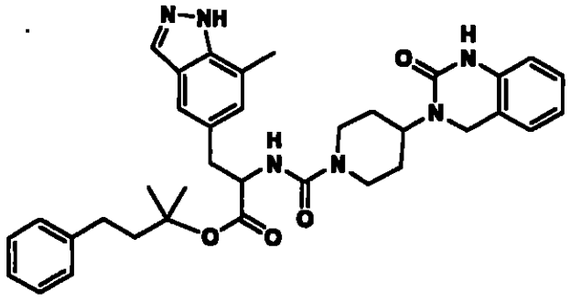
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-2-phenyl-ethyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid t-butyl ester. LC/MS: t_R=2.52 min, 609.46 $(MH)^+$.

Example 270

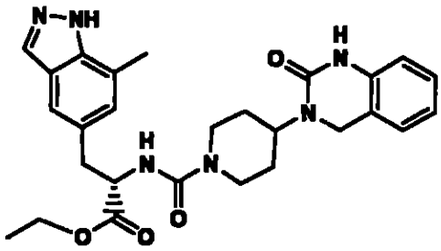
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-3-phenyl- propyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid t-butyl ester. LC/MS: t_R=2.61 min, 623.48 $(MH)^+$.

Example 271

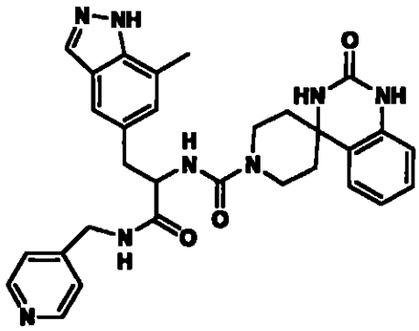
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid ethyl ester



Prepared as described above for (±)-3-(7-methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid t-butyl ester. LC/MS: t_R=1.98 min, 505.32 $(MH)^+$.

Example 272

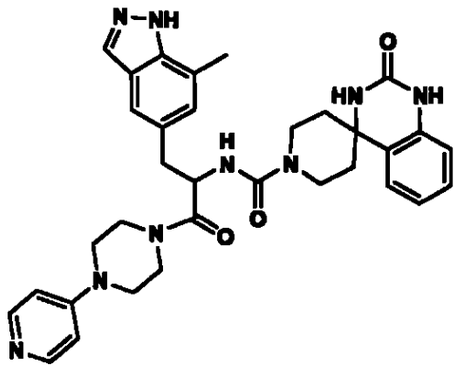
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-methyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



Prepared as described above for Example 16. LC/MS: t_R=1.49 min, 553.12 $(MH)^+$.

Example 273

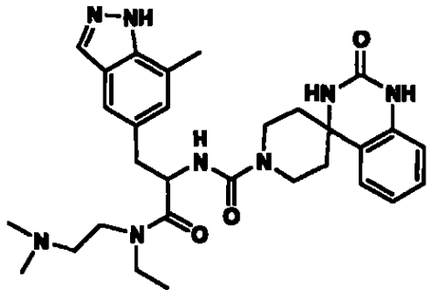
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



Prepared as described above for Example 16. LC/MS: t_R=1.56 min, 608.18 $(MH)^+$.

Example 274

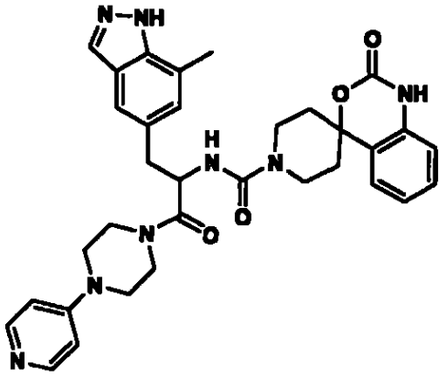
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[(2-dimethylamino-ethyl-ethyl carbamoyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



Prepared as described above for Example 16. LC/MS: t_R=1.58 min, 561.20 $(MH)^+$.

Example 275

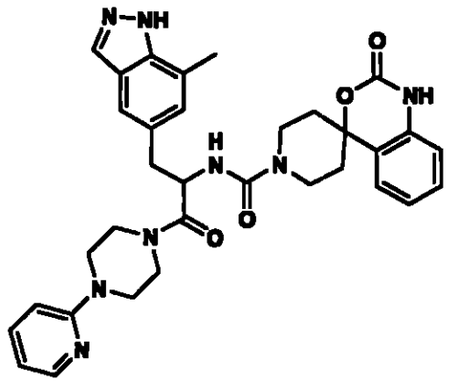
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



Prepared as described above for Example 16. LC/MS: t_R=1.56 min, 609.14 $(MH)^+$.

Example 276

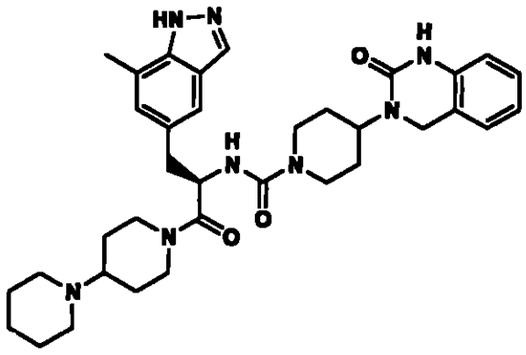
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-2-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide



Prepared as described above for Example 16. LC/MS: t_R=1.57 min, 609.17 $(MH)^+$.

Example 277

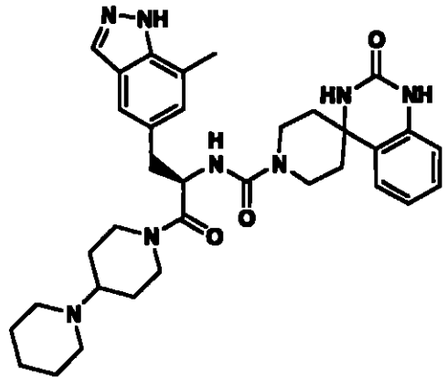
(R)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3yl)-piperidine-1d-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]amide



Prepared as described above for Example 16. ^{1}H-NMR (CD_3OD, 500 MHz) δ -0.27 (1H, m), 0.75 (1H, m), 1.1-2.0 (12H, m), 2.10 (2H, m), 2.4-2.5 (3H, m), 2.57 (3H, s), 2.68 (2H, m), 2.92 (4H, m), 3.10 (4H, m), 3.9-5.1 (4H, several m), 6.82 (1H, d), 6.96 (1H, t), 7.18 (3H, m), 7.50 (1H, s), 8.05 (1H, s). LC/MS: t_R=1.68 min, 627.42 $(MH)^+$.

Example 278

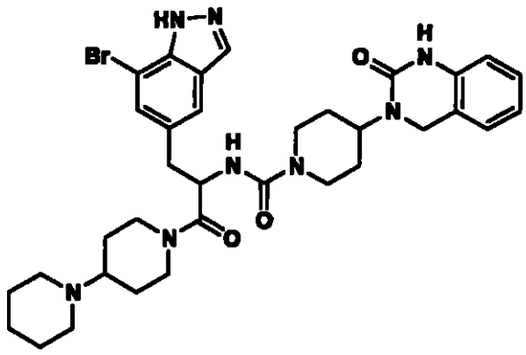
(R)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide



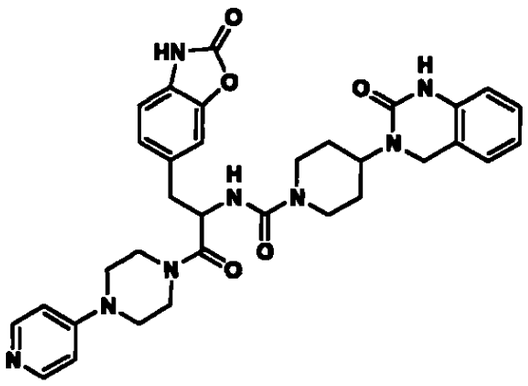
Prepared as descr ibed above for Example 16. LC/MS: t_R=1.63 min, 613.36 $(MH)^+$.

Among other compounds envisaged within the present invention and capable of being made according to the description provided herein or those methods known to those skilled in the art include the following prophetic examples:

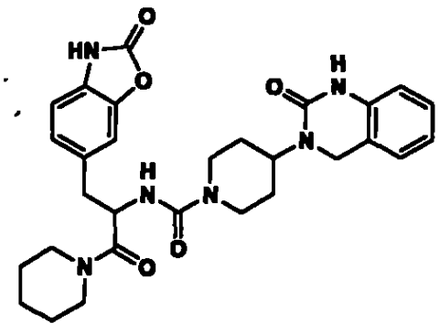
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide



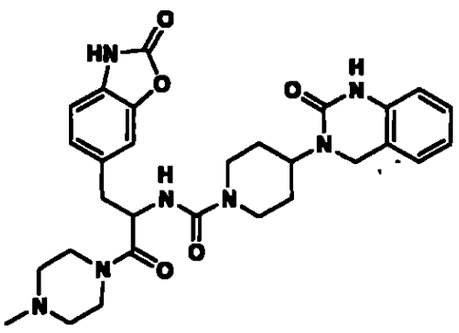
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



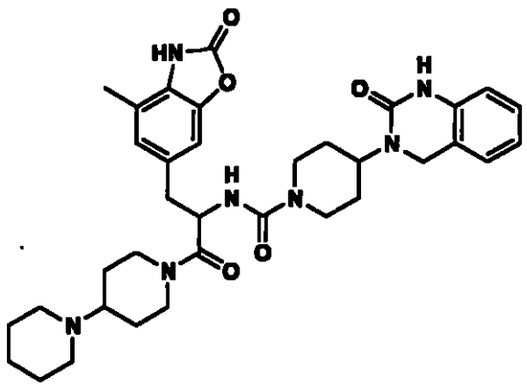
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide



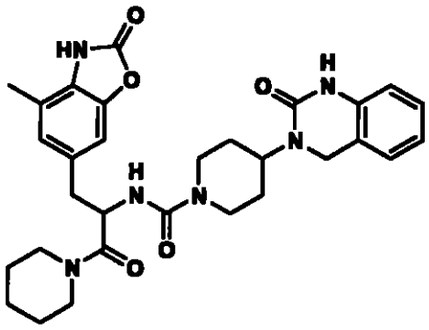
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide



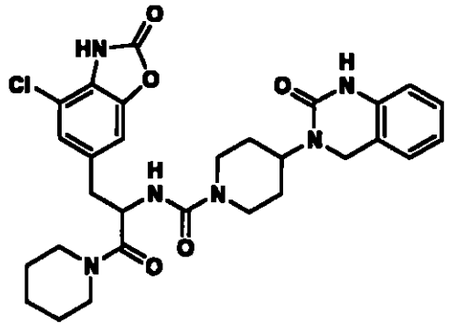
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide

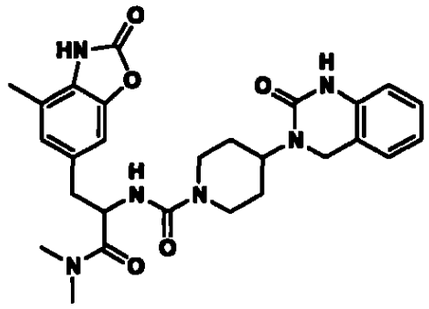


4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide

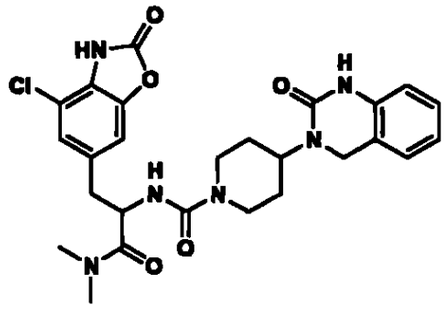


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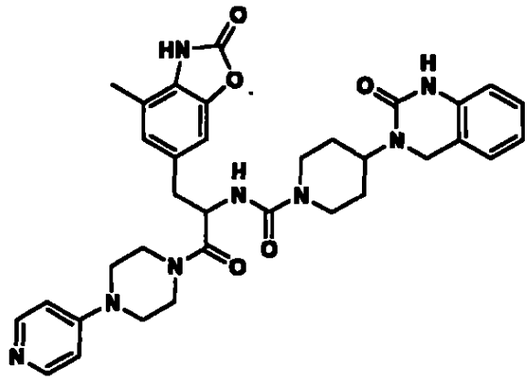
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide



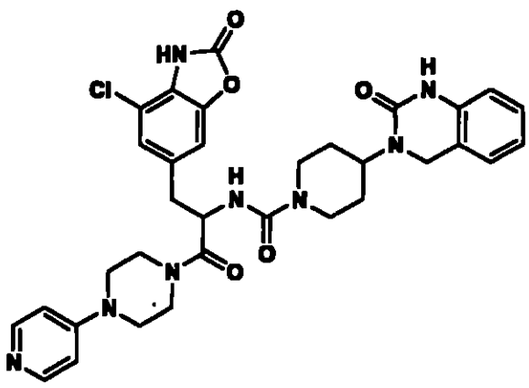
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide



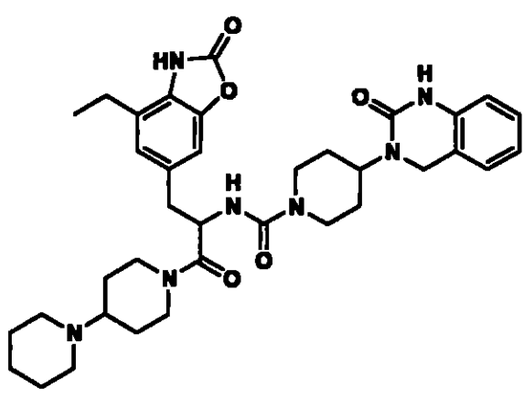
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



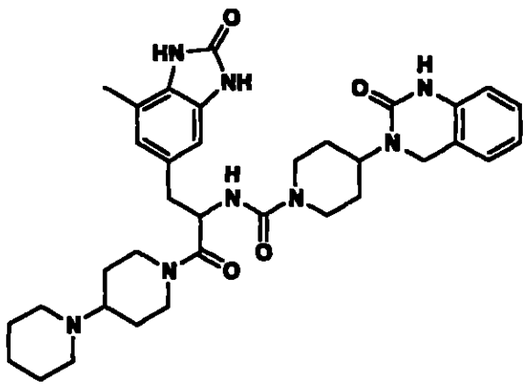
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide



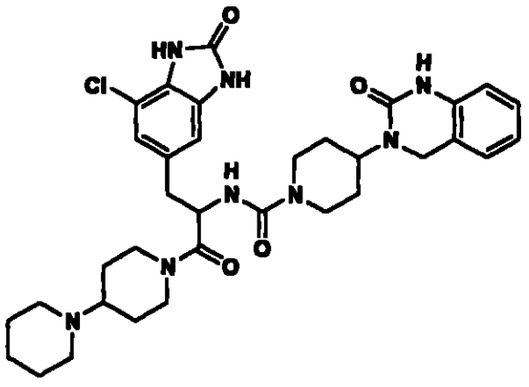
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide



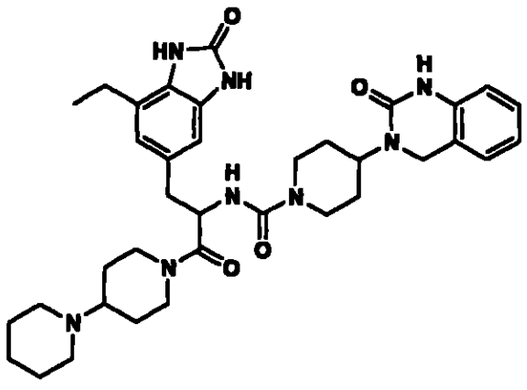
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



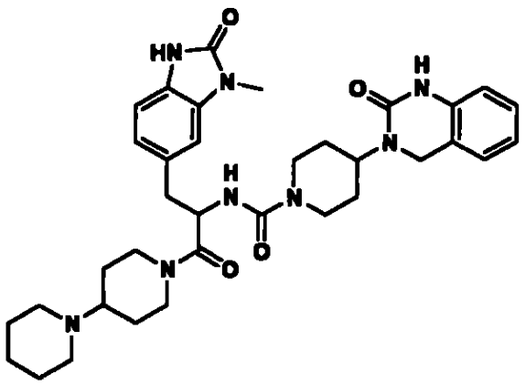
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



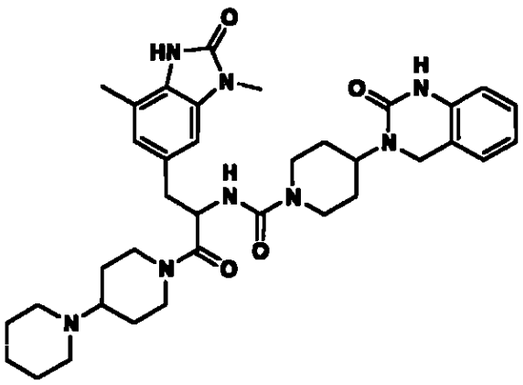
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide



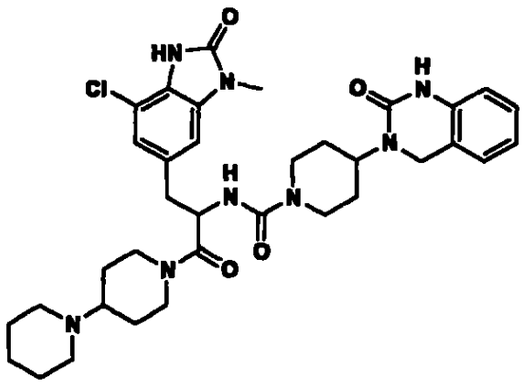
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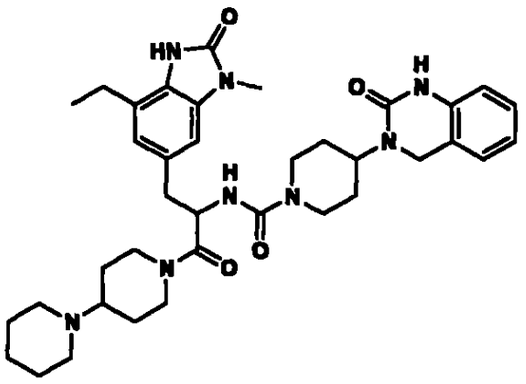
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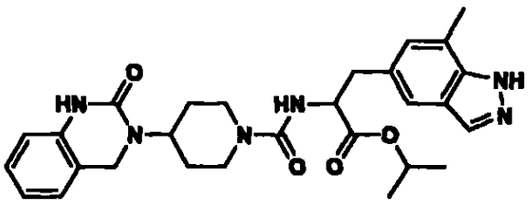
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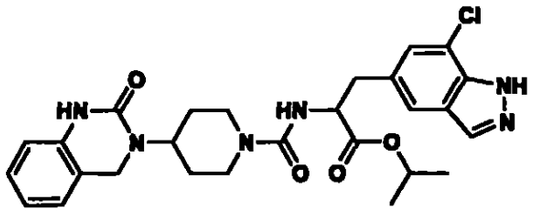
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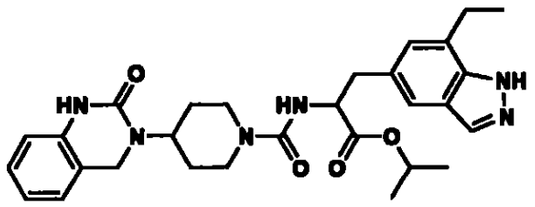
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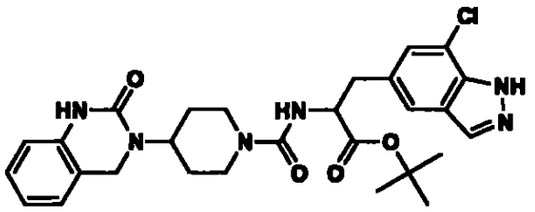
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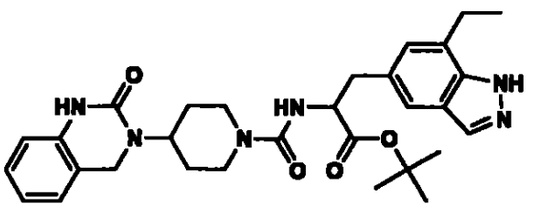
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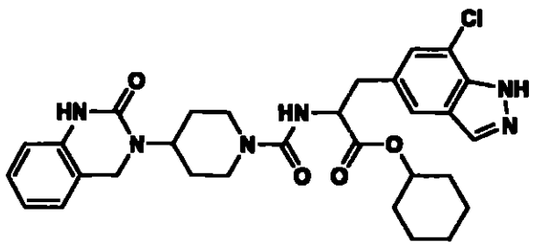
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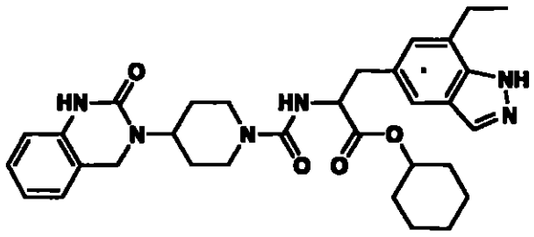
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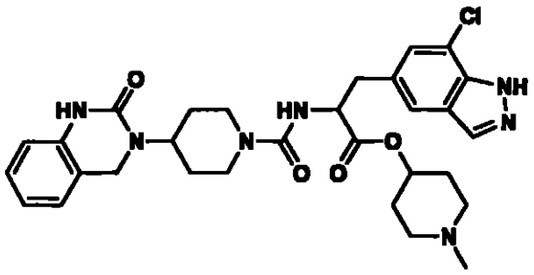
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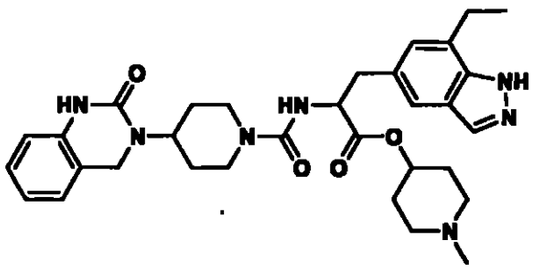
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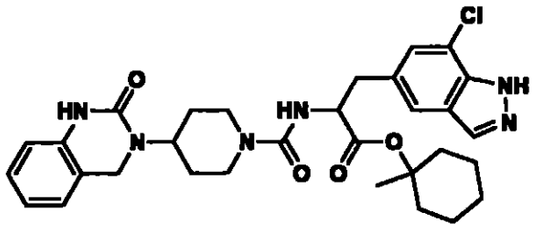
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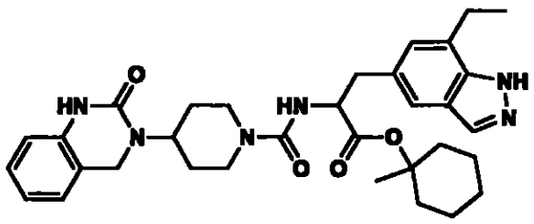
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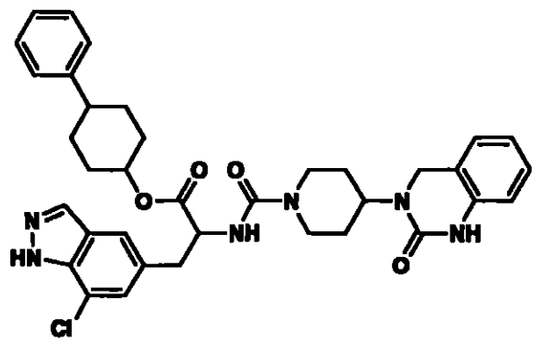
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3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester

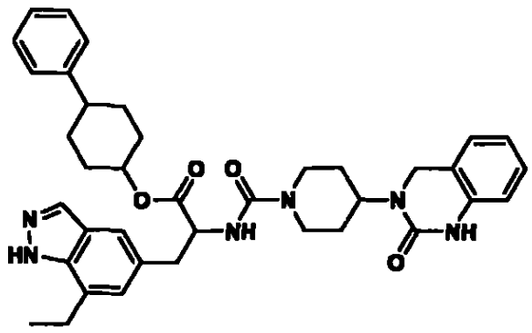


3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester



3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester

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CGRP Binding Assay

Tissue Culture. SK-N-MC cells were grown at 37 °C in 5% CO_2 as a monolayer in medium consisting of MEM with Earle's salts and L-glutamine (Gibco) supplemented with 10% fetal bovine serum (Gibco).

Cell Pellets. The cells were rinsed twice with phosphate-buffered saline (155 mM NaCl, 3.3 mM Na_2HPO_4, 1.1 mM KH_2PO_4, pH 7.4), and incubated for 5-10 min. at 4 °C in hypotonic lysis buffer consisting of 10 mM Tris (pH 7.4) and 5 mM EDTA. The cells were transferred from plates to polypropylene tubes (16 x 100 mm) and homogenized using a polytron. Homogenates were centrifuged at 32,000 x g for 30 min. The pellets were resuspended in cold hypotonic lysis buffer with 0.1% mammalian protease inhibitor cocktail (Sigma) and assayed for protein concentration. The SK-N-MC homogenate was then aliquoted and stored at -80 °C until needed.

Radioligand Binding Assay. The compounds of invention were solubilized and carried through serial dilutions using 100% DMSO. Aliquots from the compound serial dilutions were further diluted 25 fold into assay buffer (50 mM Tris-Cl pH 7.5, 5 mM $MgCl_2$, 0.005% Triton X-100) and transferred (volume 50 µl) into 96 well assay plates. [^{125}I]-CGRP (Amersham Biosciences) was diluted to 60 pM in assay buffer and a volume of 50 µl was added to each well. SK-N-MC pellets were thawed, diluted in assay buffer with fresh 0.1% mammalian protease inhibitor cocktail (Sigma), and homogenized again. SK-N-MC homogenate (5 µg/well) was added in a volume of 100 µl. The assay plates were then incubated at room temperature for 2 h. Assays were stopped by addition of excess cold wash buffer (20 mM Tris-Cl pH 7.5, 0.1% BSA) immediately followed by filtration over glass fiber filters (Whatman GF/B) previously soaked in 0. 5% PEI. Non-specific binding was defined with 1 µM beta-CGRP. Protein bound radioactivity was determined using a gamma or scintillation counter. The IC_{50} was defined as the concentration of a compound of invention required to displace 50% of radioligand binding.

In the table below, results are denoted as follows: A ≤ 10nM; 10nM < B ≤ 100 nM; 100 nM < C ≤ 1000 nM; D > 1000 nM.

Table 4. CGRP Binding, cAMP Function and Ex Vivo Human Cerebral Artery Data

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
1	C	*	*
2	A	A	A
3	B	B	B
4	B	B	*
5	A	A	*
6	A	A	A
7	C	C	*
8	C	C	*
9	B	B	*
10	C	B	*
11	B	B	*
12	B	C	*
13	C	*	*
14	D	*	*
15	C	C	*
16	A	A	A
17	A	A	A
18	A	B	A
19	A	A	A
20	A	A	A
21	A	A	A
22	A	A	*
23	A	A	A
24	B	B	*
25	A	A	A

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
26	B	B	*
27	B	C	*
28	C	*	*
29	A	*	*
30	B	*	*
31	A	A	*
32	C	*	*
33	C	*	*
34	A	A	*
35	B	B	*
36	B	B	*
37	A	B	*
38	B	B	*
39	C	C	*
40a	A	A	*
40b	B	*	*
40c	D	*	*
40d	C	*	*
40e	D	*	*
40f	D	*	*
40g	D	*	*
40h	D	*	*
40i	B	*	*
40j	D	*	*
40k	D	*	*
41a	B	*	*
41b	A	*	*
41c	A	*	*
41d	B	*	*
41e	A	*	*

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
41f	B	*	*
42	C	*	*
43	A	A	A
44	C	*	*
45	A	*	*
46	B	B	*
47	A	A	A
48	D	*	*
49	A	*	*
50	A	*	*
51	D	*	*
52	D	*	*
53	D	*	*
54	B	C	A
55	C	*	*
56	A	A	*
57	C	*	*
58	D	*	*
59	C	*	*
60	C	*	*
61	C	C	*
62	B	B	*
63	C	C	*
64	B	*	B
65	A	B	B
66	C	*	*
67	B	C	B
68	A	A	A
69	A	A	A
70	A	A	A

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
71	A	A	A
72	A	A	A
73	B	B	*
74	A	A	A
75	A	B	*
76	B	B	A
77	B	B	*
78	A	A	*
79	B	C	*
80	C	*	*
81	B	C	*
82	B	C	*
83	B	C	*
84	B	B	*
85	C	*	*
86	C	B	C
87	B	B	*
88	C	B	*
89	C	B	*
90	B	*	*
91	C	*	*
92	B	C	*
93	C	*	*
94	C	C	*
95	C	*	*
96	D	*	*
97	D	*	*
98	D	*	*
99	D	D	*
100	C	*	*

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
101	D	*	*
102	C	*	*
103	C	*	*
104	C	*	*
105	C	*	*
106	C	*	*
107	C	*	*
108	C	*	*
109	C	*	*
110	C	*	*
111	C	*	*
112	C	*	*
113	C	*	*
114	C	*	*
115	C	*	*
116	C	*	*
117	C	*	*
118	C	*	*
119	C	*	*
120	C	*	*
121	C	*	*
122	C	*	*
123	B	*	*
124	C	*	*
125	C	*	*
126	C	*	*
127	C	*	*
128	C	*	*
129	C	*	*
130	C	*	*

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
131	C	*	*
132	C	*	*
133	C	*	*
134	C	*	*
135	C	*	*
136	C	*	*
137	C	*	*
138	C	*	*
139	C	*	*
140	B	*	*
141	C	*	*
142	C	*	*
143	C	*	*
144	C	*	*
145	C	*	*
146	B	*	*
147	C	*	*
148	B	*	*
149	B	*	*
150	B	*	*
151	C	*	*
152	C	*	*
153	C	*	*
154	C	*	*
155	C	*	*
156	C	*	*
157	C	*	*
158	B	*	*
159	B	*	*
160	C	*	*

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
161	B	*	*
162	C	*	*
163	C	*	*
164	C	*	*
165	C	*	*
166	C	*	*
167	C	*	*
168	C	*	*
169	C	*	*
170	C	*	*
171	B	*	*
172	B	*	*
173	C	*	*
174	C	*	*
175	C	*	*
176	B	*	*
177	B	*	*
178	B	*	*
179	C	*	*
180	C	*	*
181	C	*	*
182	C	*	*
183	C	*	*
184	B	*	*
185	C	*	*
186	C	*	*
187	C	*	*
188	C	*	*
189	C	*	*
190	C	*	*

Example #	CGRP binding[1] IC_{50} (nM)	cAMP Function[2] IC_{50} (nM)	Cerebral Artery[3] EC_{50} (nM)
191	C	*	*
192	C	*	*
193	B	*	*
194	C	*	*
195	C	*	*
196	B	*	*
197	C	*	*
198	C	*	*
199	B	*	*
200	B	*	*
201	C	*	*

Cyclic AMP Assay

Functional Antagonism. Antagonism of the compounds of invention was determined by measuring the formation of cyclic AMP (adenosine 3'5'-cyclic monophosphate) in SK-N-MC cells that endogenously express the human CGRP receptor. CGRP receptor complex is coupled with Gs protein and CGRP binding to this complex leads to the cyclic AMP production via Gs - dependent activation of an adenylate cyclase (Juaneda C et al., TiPS, 2000; 21:432-438; incorporated by reference herein). Consequently, CGRP receptor antagonists inhibit CGRP – induced cyclic AMP formation in SK-N-MC cells (Doods H et al., Br J Pharmacol,2000; 129(3):420-423) ; incorporated by reference herein). For cyclic AMP measurements SK-N-MC cells were incubated with 0.3 nM CGRP alone or in the presence of various concentrations of the compounds of invention for 30 min at room temperature. Compounds of invention were pre-incubated with SK-N-MC cells for 15 min before the addition of CGRP to allow receptor occupancy (Edvinsson et al., Eur J Pharmacol, 2001, 415:39-44; incorporated by reference herein). Cyclic AMP was extracted using the lysis reagent and its concentration was determined by radioimmunoassay using RPA559 cAMP SPA Direct Screening Assay Kit (Amersham Pharmacia Biotech). IC50 values were calculated using Excel fit. The tested compounds of invention were determined

to be antagonists as they exhibited a dose – dependent inhibition of the CGRP – induced cyclic AMP production. See Table 3 for summary of results.

Schild Analysis. Schild analysis can be used to characterize the nature of antagonism of the compounds of invention. The dose response of CGRP stimulated cAMP production was generated either with CGRP alone, or in the presence of various concentrations of compounds of invention. The antagonist dose is plotted as X against the dose ratio (defined as IC50 of agonist with the presence of the compounds divided by the IC50 of the agonist alone) minus 1 as Y. Linear regression was then performed with both X and Y axis log-transformed. A slope that does not differ significantly from unity (1) indicates competitive antagonism. K_b is the dissociation constant of the antagonist.

Table 5. Schild Analysis

Example #	K_b(nM)	slope
2	0.16	0.94
3	55	0.96
5	3	0.92
6	0.36	0.93
16		1.3
17	1.1	0.92
18	1	0.8
21	0.018	0.89
43	0.018	1.2
45		1.4
47	0.1	0.93
69	0.016	1
70		0.71
71	2	0.87

See Figure 1. Schild Analysis.

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Ex Vivo Human Cerebral Artery Assay

Rationale and Overview. To provided direct evidence of the ability for novel compounds to reverse CGRP-induced dilation in human cerebral vessels, an ex vivo assay was designed. Briefly, isolated vessel rings were mounted in a tissue bath where vessels were pre-contracted with potassium chloride (KCl) and fully dilated with hCGRP, then this relaxation was reversed by the cumulative addition of CGRP-receptor antagonists (complete details follow).

Tissue Samples. Autopsy samples of human arteries were obtained from vendors (ABS Inc. or NDRI). All vessels were transported on ice-cold HEPES buffer (composition in mM: NaCl 130, KCl 4, KH2PO4 1.2, MgSO4 1.2, CaCl2 1.8, Glucose 6, NaHCO3 4, HEPES 10, EDTA 0.025). Upon receipt, the vessels were placed in cold Kreb's buffer (composition in mM: NaCl 118.4, KCl 4.7, KH2PO4 1.2, MgSO4 1.2, CaCl2 1.8, Glucose 10.1, NaHCO3 25) saturated with carbogen (5% CO2 and 95 % oxygen).

Isolated Tissue Baths. The vessels were cleaned of connective tissues and cut into cylindrical segments of 4-5mm in length. The vessels were then mounted in tissue baths between two stainless steel hooks; one of which is fixed and the other of which was connected to a force displacement transducer. The vessel tension was continuously recorded using a data acquisition system (Powerlab, ADInstruments, Mountain View, CA) connected to the transducer. The tissue baths containing Krebs buffer and mounted vessels were temperature (37 °C) and pH (7.4) controlled with continuous bubbling of carbogen. The artery segments were allowed to equilibrate for about 30-45 min until a stable resting tone was achieved. Prior to the assay, vessels were primed (conditioned) with 100 mM KCl and subsequently washed. The vessels were pre-contracted with 10 mM KCl and fully dilated with 1 nM hCGRP. Concentration-response curves to CGRP-receptor antagonists were performed by the cumulative addition of drugs in half log units in fully dilated vessels. At each concentration, the effects of the drugs were expressed as % reversal of CGRP-induced relaxation in each vessel. The actual assay and data analysis were performed for each vessel individually, fitting the concentration-response data to a four

parameter logistic function by non-linear regression analysis, to estimate the EC50 values. A summary of results is provided in Table 3.

Non-Terminal Method for Assessing In Vivo Efficacy of Small Molecule CGRP-receptor antagonists in Mammals

Overview. Blocking cerebral artery dilation induced by calcitonin gene-related peptide (CGRP) has been proposed as a treatment for migraine headache, however, novel small molecule CGRP-receptor antagonists have shown species-specific differences with relatively poor activity in rodents (Mallee et al. J Biol Chem 2002 277:14294) requiring new models for assessment of in vivo efficacy. Non-human primates (e.g., marmosets) are the only animals known to have human-like CGRP receptor pharmacology conferred by the presence of the specific amino acid residue (Trp74) in their RAMP1 sequence which is responsible for the phenotype of the human receptor (Mallee et al. J Biol Chem 2002 277:14294). Since current migraine models primarily use rats (Escott et al. Brain Res 1995 669:93; Williamson et al. Cephalalgia 1997 17:525), or are invasive, terminal procedures in primates (Doods et al. Br J Pharmacol 2000 129:420), a novel non-invasive, survival model in non-human primates for in vivo efficacy assessment of CGRP-receptor antagonists as in the present invention is a significant contribution. While it is known that trigeminal activation increases both cerebral (Goadsby & Edvinsson, 1993) and facial blood flow (Doods et al., 2000), demonstration of a direct relationship between facial blood flow and cerebral artery dilation conducted in the same animals was not known. Therefore, before initiating studies in non-human primates, laser Doppler measurement of facial blood flow was directly validated in the rat as a surrogate for cerebral artery dilation in terminal studies that measured both cerebral artery diameter and changes in facial blood flow in the same animals (see Figure 2. Direct Validation of Facial Blood Flow as Surrogate for Cerebral Artery Dilation in the Rat). In both measures, comparable increases were induced by i.v. CGRP and blocked by the peptide antagonist hαCGRP(8-37). Next, the method of i.v. CGRP-induced changes in facial blood flow was validated as a recovery model in isoflurane anesthetized rats using hαCGRP(8-37). The survival method was then established in non-human primates and a dose-response study characterizing i.v. CGRP activity was

completed (see Figure 3. Dose-Response for haCGRP in Non-Human-Primate Laser Doppler Facial Blood Flow). Peptide and small-molecule CGRP-receptor antagonists were used to validate the non-human primate model. Pre-treatment with small molecule antagonists or haCGRP(8-37) dose-dependently inhibited i.v. CGRP-stimulated increases in primate facial blood flow (see Figure 4. Inhibitition of CGRP-Induced Changes in Non-Human Primate Facial Blood Flow), without altering blood pressure (see Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure). Post-treatment of antagonists also reversed CGRP-induced increases in facial blood flow (not shown). This survival model provides a novel, non-invasive recovery procedure for evaluating prophylactic and abortive effects of CGRP-receptor antagonists in non-human primates, or in transgenic animals with humanized RAMP1 (Trp74) which have similar CGRP receptor pharmacology, as a surrogate marker for activity in cerebral vessel diameter.

Animals. Adult male and female common marmosets (Callithrix jacchus) purchased from Harlan and weighing 350-550 g served as subjects. Other mammals endogenously expressing RAMP1 having Trp 74 or transgenic mammals with humanized RAMP1 having Trp 74 can also be employed in the method described herein.

Anesthesia & Surgical Preparation. Animals are anesthetized by isoflurane inhalation in an induction chamber (4-5% rapid induction, maintained with 1-2.5%; Solomon et al., 1999). Anesthesia is maintained by delivering a constant supply of air:oxygen (50:50) and isoflurane via face mask, or by intubation and ventilation (with blood gas monitoring). Body temperature is maintained at 38 ± 0.5 °C by placement on an automated temperature controlled surface with rectal probe. A small area of fur (approx. 1.5 cm square) is removed from one or both sides of the face by application of a depilatory cream and/or shaving. Surgical areas are clipped and prepared with betadine. An i.v. line is placed in any accessible vein for the administration of test compounds and CGRP-receptor agonist and, if needed, withdrawal of blood samples (max 2.5 ml, 10%) for blood gas monitoring and content analysis. A solution of 5% dextrose is administered i.v. in order to maintain blood sugar levels. Anesthesia depth is monitored by measuring blood pressure and

heart rate using a non-invasive arm cuff method and a pulse oximeter, respectively. Guanethidine 5-10 mg/kg i.v., supplemented with 5 mg/kg i.v. as needed, may be given to stabilize the peak flux in facial blood flow seen with repeated stimulation-induced changes in blood flow (Escott et al., 1999; incorporated by reference herein). Microvascular blood flow is monitored by attaching a self adhesive laser Doppler flow probe to the facial skin.

Compound Administration Test compounds may be administered i.v. (0.01–5 ml/kg), i.m. (0.01–0.5 ml/kg), s.c. (0.01–5 ml/kg) or p.o. (0.1–10 ml/kg) (Diehl et al., 2001; incorporated by reference herein). CGRP-receptor agonists may be delivered i.v. (0.01–5 ml/kg), i.d. (10–100 µl/site) or s.c. (10–100 µl/site).

Laser Doppler Flowmetry A control increase in facial blood flow is induced by administration of a vasodilator, such as CGRP (0.05–100 µg/kg i.v.) or 2–20 pmol/site i.d) or adrenomedullin (ADM, 0.05–5 mg/kg i.v. or 10–100 pmol/site i.d.). Test compound or vehicle is administered either before (pre-treatment) or after (post-treatment) subsequent repeat administration of the vasodilating agent, providing the ability to assess prophylactic or therapeutic actions. Blood pressure is monitored continuously to ensure adequate depth of anesthesia, and anesthetic is adjusted to maintain stable levels that match pre-treatment values. During collection of laser Doppler flowmetry data, isoflurane may be reduced to 0.25-0.75% as previous electrophysiologic studies in marmosets found that recordings were sensitive to isoflurane concentration (Solomon, 1999; incorporated by reference herein). To reduce the number of animals used, the effect of test compound on i.v. vasodilator-induced changes in blood flow may be repeated up to 6 times in a single session.

Recovery Animals are returned to the transport cage which is placed on a temperature controlled surface to keep the animals warm until fully awake and ambulatory. Animals may be tested again after 7-14 days rest, and may be tested repeatedly at 7-14 day intervals depending on the health of the animal.

See Diehl KH, Hull R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C. A good practice guide to the administration of substances

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and removal of blood, including routes and volumes. J Appl Toxicol. 2001 Jan-Feb;21(1):15-23; Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP-receptor antagonist. Br J Pharmacol. 2000 Feb;129(3):420-3; Edvinsson L. Calcitonin gene-related peptide (CGRP) and the pathophysiology of headache: therapeutic implications. CNS Drugs 2001;15(10):745-53; Escott KJ, Beattie DT, Connor HE, Brain SD. Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide. Brain Res. 1995 Jan 9;669(1):93-9; Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 1993 Jan;33(1):48-56; Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olsen J. CGRP may play a causative role in migraine. Cephalalgia, 2002, 22, 54-61; Mallee JJ, Salvatore CA, LeBourdelles B, Oliver KR, Longmore J, Koblan KS, Kane SA. RAMP1 determines the species selectivity of non-peptide CGRP receptor antagonists. J Biol Chem. 2002 Feb 14 [epub ahead of print]; Solomon SG, White AJ, Martin PR. Temporal contrast sensitivity in the lateral geniculate nucleus of a New World monkey, the marmoset Callithrix jacchus. J Physiol. 1999 Jun 15;517 (Pt 3):907-17; all incorporated by reference herein.

Departures from Other Migraine Models. This invention represents a novel migraine model and is remarkably distinct from other migraine models. Some of the distinguishing characteristics of the method of the present invention include: (i) the only survival model of migraine in any species; (ii) the only model to demonstrate the abortive (post-treatment) effects of CGRP antagonists on active induced increases in blood flow; (iii) the only demonstration of a direct relationship between facial blood flow and intracranial artery dilation carried out in the same animals; (iv) the only model to use non-invasive surgical techniques, and does not require catheter placement, intubation, or neuromuscular blockade; (v) the only primate model to use exogenous CGRP as the stimulus and demonstrate pretreatment blockade by CGRP antagonism and post-treatment reversal by CGRP antagonism; (vi) the only migraine model to use isoflurane anesthesia in spontaneously breathing animals. The models described in Williamson et al., Sumatriptan inhibits neurogenic vasodilation of dural blood vessels in the anaesthetized rat-intravital microscope studies. Cephalalgia.

1997 Jun;17(4):525-31; Williamson DJ, Hargreaves RJ, Hill RG, Shepheard SL. Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide on dural vessel diameter in the anaesthetized rat. Cephalalgia. 1997 Jun;17(4):518-24; Escott KJ et al., Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide. Brain Res. 1995 Jan 9;669(1):93-9; Chu DQ et al., The calcitonin gene-related peptide (CGRP) antagonist CGRP(8-37) blocks vasodilatation in inflamed rat skin: involvement of adrenomedullin in addition to CGRP. Neurosci Lett. 2001 Sep 14;310(2-3):169-72; Escott KJ, Brain SD. Effect of a calcitonin gene-related peptide antagonist (CGRP8-37) on skin vasodilatation and oedema induced by stimulation of the rat saphenous nerve. Br J Pharmacol. 1993 Oct;110(2):772-6; Hall JM, Siney L, Lippton H, Hyman A, Kang-Chang J, Brain SD. Interaction of human adrenomedullin 13-52 with calcitonin gene-related peptide receptors in the microvasculature of the rat and hamster. Br J Pharmacol. 1995 Feb;114(3):592-7; Hall JM, Brain SD. Interaction of amylin with calcitonin gene-related peptide receptors in the microvasculature of the hamster cheek pouch in vivo. Br J Pharmacol. 1999 Jan;126(1):280-4; and Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP-receptor antagonist. Br J Pharmacol. 2000 Feb;129(3):420-3 fail to possess the remarkable features of the method of the present invention.

In the table below, results are denoted as follows: W ≤ 25%; 25% < X ≤ 50%; 50% < Y ≤ 75%; Z > 75%.

Table 6. Inhibition of CGRP-Induced Increase in Laser Doppler Facial Blood Flow in the Non-Human Primate (e.g., Common Marmoset)

	Non-Human Primate (% Inhibition) of CGRP-induced (10 μg/kg, iv) increase in laser Doppler facial blood flow				
Example #	0.01 mg/kg, iv	0.03 mg/kg, iv	0.1 mg/kg, iv	0.3 mg/kg, iv	1 mg/kg, iv
2	W	X	X	Y	Z
6					Z
16		Y			
69		Y	Z		
hαCGRP (8-37)					Z
	W ≤ 25%; 25% < X ≤ 50%; 50% < Y ≤ 75%; Z > 75%.				

See Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure.

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What is claimed is:

1. A compound selected from the group consisting of

(±)-3-(3-Cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-cyano-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(3-cyano-7-methyl-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-3-(7-Isopropyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-isopropyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-3-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-2-[4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carbonyl]-amino]-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester;

(±)-4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(2-Oxo-1,2,4,5-tetrahydro-benzo[d][1,3]diazepin-3-yl-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(6-Hydroxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Methoxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Chloro-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-3-methyl1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-7,7-dimethyl-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-methyl-1H-indazol-5-yl)propanoate;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(4-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(2-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-o-tolylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-ethyl-3-methyl-1H-indazol-5-yl)propanoate;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-8'-fluoro-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2,4-dioxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2-(trifluoromethyl)-1*H*-benzo[d]imidazol-5-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

(*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(2',3'-dihydro-2'-oxospiro(piperidine-4,4'-(1*H*)-quinazoline)carboxamide;

4-(1,2-dihydro-2,4-dioxoquinazolin-3(4*H*)-yl)-*N*-((*R*)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-isopropyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2 H-quinazolin-3-yl)-piperidin-1-yl]-butyramide;

(±)-Phenyl-acetic acid N'-{2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyryl}-hydrazide;

(±)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(8-fluoro-2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(7-methyl-1H-indazol-5-ylmethyl)-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline]-butane-1,4-dione;

(±)-1-(4-Cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;

(±)-1-(4-cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl cyclohexyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid piperidin-4-yl ester;
(±)-4-(3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyloxy)-piperidine-1-carboxylic acid tert-butyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-diethylamino-1-methyl-ethyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-2-phenyl-ethyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-3-phenyl- propyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid ethyl ester;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-methyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[(2-dimethylamino-ethyl-ethyl carbamoyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-2-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3yl)-piperidine-1d-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]amide; and
(*R*)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-

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dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide or a pharmaceutically acceptable salt or solvate thereof.

2. A compound selected from the group consisting of

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester; and
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester or a pharmaceutically acceptable salt or solvate thereof.

3. A pharmaceutical composition comprising a compound selected from the group consisting of
(±)-3-(3-Cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-cyano-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(3-cyano-7-methyl-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-3-(7-Isopropyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-isopropyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-3-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;

(±)-2-[4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carbonyl]-amino]-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester;

(±)-4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(2-Oxo-1,2,4,5-tetrahydro-benzo[d][1,3]diazepin-3-yl-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(6-Hydroxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Methoxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Chloro-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-3-methyl1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-7,7-dimethyl-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-methyl-1H-indazol-5-yl)propanoate;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(4-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(2-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-o-tolylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-ethyl-3-methyl-1H-indazol-5-yl)propanoate;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-8'-fluoro-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2,4-dioxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2-(trifluoromethyl)-1*H*-benzo[d]imidazol-5-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

(*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(2',3'-dihydro-2'-oxospiro(piperidine-4,4'-(1*H*)-quinazoline)carboxamide;

4-(1,2-dihydro-2,4-dioxoquinazolin-3(4*H*)-yl)-*N*-((*R*)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-isopropyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

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(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2 H-quinazolin-3-yl)-piperidin-1-yl]-butyramide;

(±)-Phenyl-acetic acid N'-{2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyryl}-hydrazide;

(±)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(8-fluoro-2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(7-methyl-1H-indazol-5-ylmethyl)-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline]-butane-1,4-dione;
(±)-1-(4-Cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;
(±)-1-(4-cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[4-(4-fluoro-phenyl)-piperazin-1-yl]-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl cyclohexyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid piperidin-4-yl ester;
(±)-4-(3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyloxy)-piperidine-1-carboxylic acid tert-butyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-diethylamino-1-methyl-ethyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-2-phenyl-ethyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-3-phenyl- propyl ester;
(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid ethyl ester;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-methyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[(2-dimethylamino-ethyl-ethyl carbamoyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;
(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-2-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3yl)-piperidine-1d-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]amide; and
(*R*)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide or a pharmaceutically acceptable salt or solvate thereof.

4. A pharmaceutical composition comprising a compound selected from the group consisting of
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

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4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;

3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;

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3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester; and
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester or a pharmaceutically acceptable salt or solvate thereof.

5. Use of a compound selected from the group consisting of
(±)-3-(3-Cyano-1H-indol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-cyano-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(3-cyano-7-methyl-1H-indol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-3-(7-Isopropyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid methyl ester;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-isopropyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-4-(2,2-Dioxo-1,4-dihydro-2H-2λ^6-benzo[1,2,6]thiadiazin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1(7-ethyl-3-methyl-1H-indazol-5-yl-methyl)-2-oxo-ethyl]-amide;
(±)-2-[4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carbonyl]-amino]-3-(7-methyl-1H-indazol-5-yl)-propionic acid methyl ester;
(±)-4-(6-Cyano-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(2-Oxo-1,2,4,5-tetrahydro-benzo[d][1,3]diazepin-3-yl-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(6-Hydroxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Methoxy-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-4-(8-Chloro-2-oxo-1,4-dihydro-2H-qinazolin-3-yl)-piperidine-1-carboxylic acid {2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-yl methyl)-2-oxo-ethyl}-amide;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-3-methyl1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Ethyl-1H-indazol-5-yl)-1-(6,7-dihydro-7,7-dimethyl-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)-1-oxopropan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-methyl-1H-indazol-5-yl)propanoate;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-phenylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(4-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(1-(4-(2-fluorophenyl)piperazin-1-yl)-3-(7-methyl-1H-indazol-5-yl)-1-oxopropan-2-yl)piperidine-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-o-tolylpiperazin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(±)-Methyl 2-(4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamido)-3-(7-ethyl-3-methyl-1H-indazol-5-yl)propanoate;

(±)-*N*-(3-(7-Ethyl-3-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(8-fluoro-1,2-dihydro-2-oxoquinazolin-3(4H)-yl)piperidine-1-carboxamide;

(±)-*N*-(3-(7-Methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-8'-fluoro-2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)-1-carboxamide;

(±)-4-(8-Fluoro-1,2-dihydro-2,4-dioxoquinazolin-3(4H)-yl)-*N*-(3-(7-methyl-1H-indazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2-(trifluoromethyl)-1*H*-benzo[d]imidazol-5-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

(*R*)-methyl 2-(4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamido)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)propanoate;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-1-(dimethylcarbamoyl)-2-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)ethyl)-4-(1,2-dihydro-2-oxoquinazolin-3(4*H*)-yl)piperidine-1-carboxamide;

N-((*R*)-3-(2,3-dihydro-2-oxo-1*H*-benzo[*d*]imidazol-6-yl)-1-oxo-1(4-piperidin-1-yl)piperidine-1-yl)propan-2-yl)-4-(2',3'-dihydro-2'-oxospiro(piperidine-4,4'-(1*H*)-quinazoline)carboxamide;

4-(1,2-dihydro-2,4-dioxoquinazolin-3(4*H*)-yl)-*N*-((*R*)-3-(7-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)piperidine-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-isopropyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-benzo[d][1,3]oxazine)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(piperidin-1-yl)piperidin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(cyclohex-1-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-*N*-((*R*)-3-(2-Oxo-2,3-dihydro-benzooxazol-6-yl)-1-oxo-1-(4-(prop-2-yl)piperazin-1-yl)propan-2-yl)-2,4-dihydro-2'-oxospiro-(piperidine-4,4'-1H-quinazoline)-1-carboxamide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(5-bromo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-iodo-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide;

(±)-*N*-(1-Benzyl-2-hydroxy-ethyl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2 H-quinazolin-3-yl)-piperidin-1-yl]-butyramide;

(±)-Phenyl-acetic acid N'-{2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyryl}-hydrazide;

(±)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(8-fluoro-2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(7-methyl-1H-indazol-5-ylmethyl)-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline]-butane-1,4-dione;

(±)-1-(4-Cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione;

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;

(±)-1-(4-cyclohexyl-piperazin-1-yl)-2-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-4-[2',3'-dihydro-2'-oxospiro-(piperidine-4,4'-quinazoline)]-butane-1,4-dione;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-cyclohexyl-piperazin-1-yl)-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;

(±)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[4-(4-

fluoro-phenyl)-piperazin-1-yl]-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl cyclohexyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-aza-bicyclo[2.2.2]oct-3-yl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid piperidin-4-yl ester;

(±)-4-(3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionyloxy)-piperidine-1-carboxylic acid tert-butyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 3,4,5,6-tetrahydro-2H-[1,4']bipyridinyl-4-yl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-diethylamino-1-methyl-ethyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-2-phenyl-ethyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1,1-dimethyl-3-phenyl- propyl ester;

(±)-3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid ethyl ester;

(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-methyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;

(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;

(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[(2-dimethylamino-ethyl-ethyl carbamoyl)-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide;

(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-4-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;

(±)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1-pyridin-2-yl-piperazinyl]-2-oxoethyl]-1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidine]-1-carboxamide;
(*R*)-4-(2-Oxo-1,4-dihydro-2H-quinazolin-3yl)-piperidine-1d-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-1H-indazol-5-ylmethyl)-2-oxo-ethyl]amide;
and
(*R*)-1-(7-Methyl-1H-indazol-5-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-2'-oxospiro-[piperidine-4,4'-(1H)-quinazoline]-1-carboxamide or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prevention of migraine.

6. Use of a compound selected from the group consisting of
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-bromo-1H-indazol-5-ylmethyl)-2-oxo-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-piperidin-1-yl-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-1-(2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-dimethylcarbamoyl-2-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl)-ethyl]-amide;
4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-yl)-1-dimethylcarbamoyl-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-methyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [1-(4-chloro-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-2-(4-pyridin-4-yl-piperazin-1-yl)-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(4-ethyl-2-oxo-2,3-dihydro-benzooxazol-6-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-chloro-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

4-(2-Oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carboxylic acid [2-[1,4']bipiperidinyl-1'-yl-1-(7-ethyl-3-methyl-2-oxo-2,3-dihydro-1H-benzoimidazol-5-ylmethyl)-2-oxo-ethyl]-amide;

3-(7-Methyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;

3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid isopropyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid tert-butyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid cyclohexyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-piperidin-4-yl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 1-methyl-cyclohexyl ester;
3-(7-Chloro-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester; and
3-(7-Ethyl-1H-indazol-5-yl)-2-{[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidine-1-carbonyl]-amino}-propionic acid 4-phenyl-cyclohexyl ester or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prevention of migraine.

Figure 1. Schild Analysis

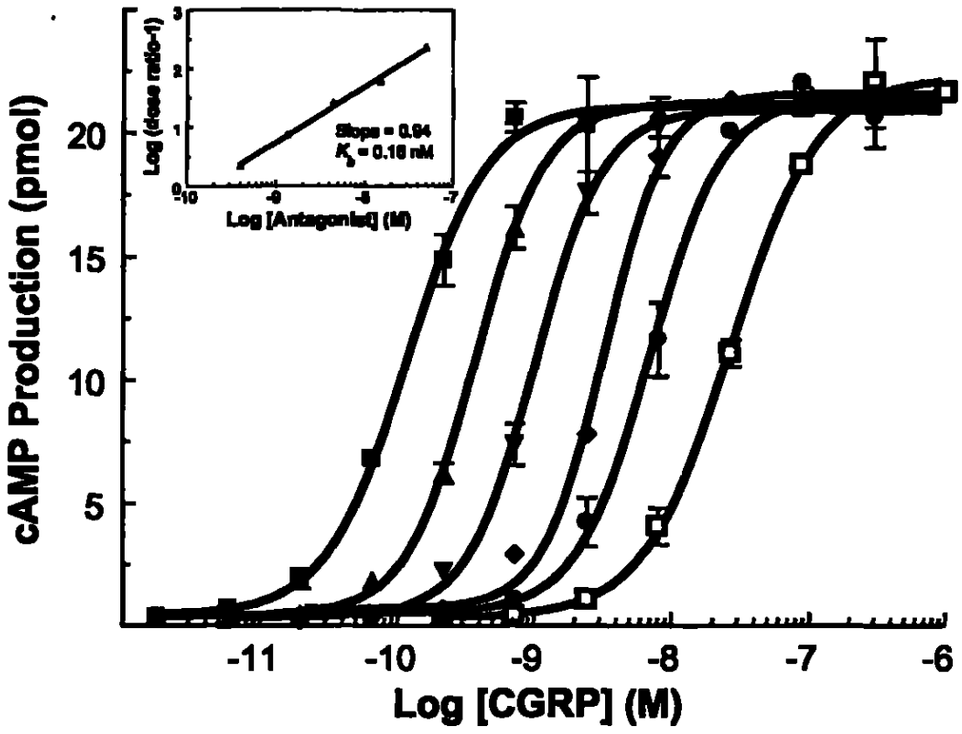


Figure 2. Direct Validation of Facial Blood Flow as Surrogate for Intracranial Artery Dilation in the Rat

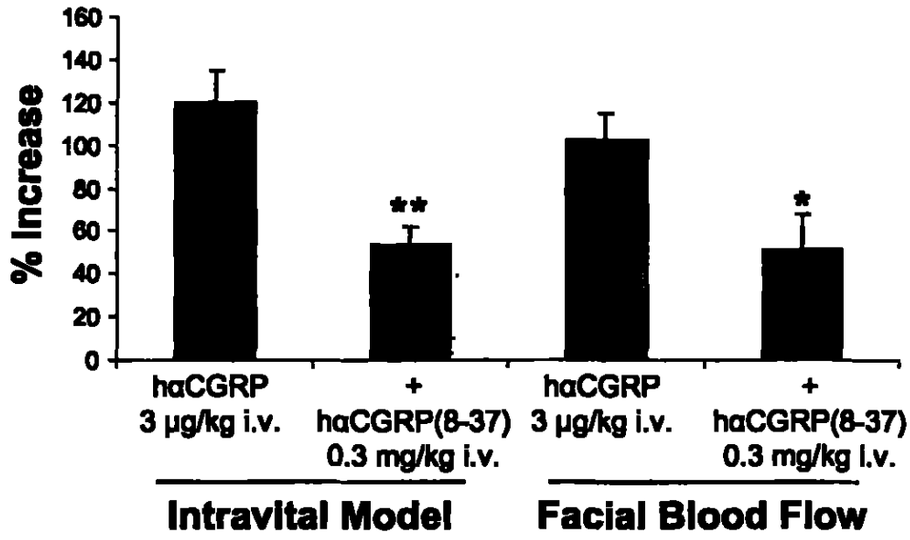


Figure 3. Dose-Response for hαCGRP in Non-Human-Primate Laser Doppler Facial Blood Flow.

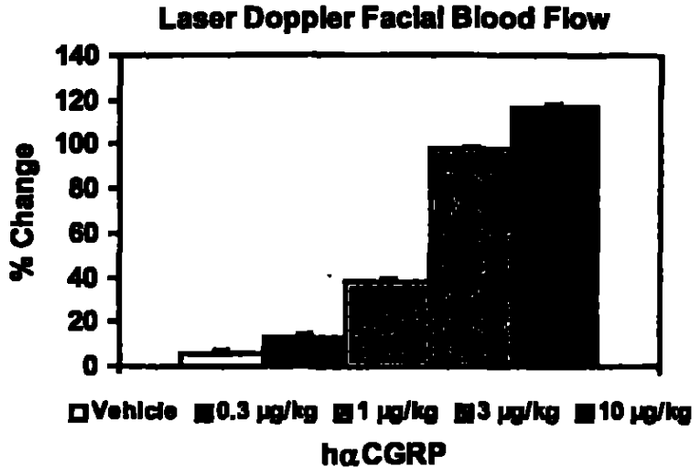
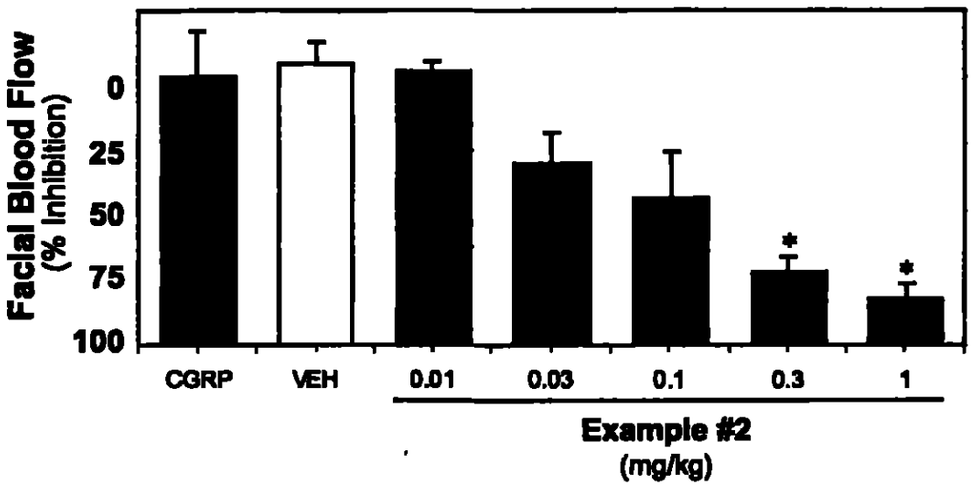
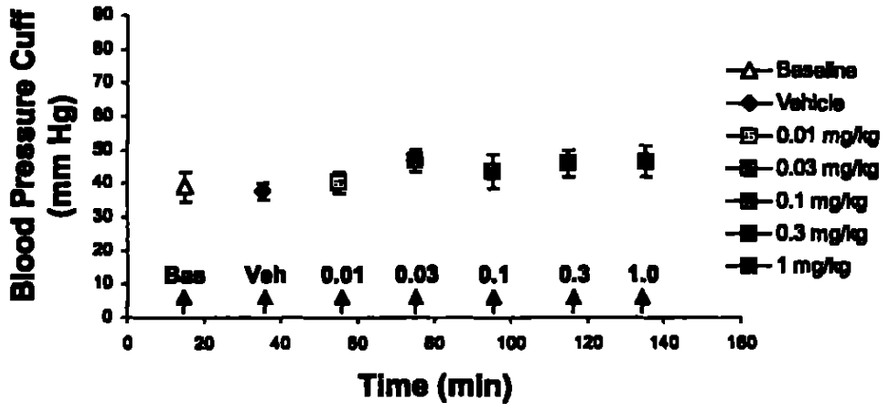


Figure 4. Inhibitition of CGRP-Induced Changes in Non-Human Primate Facial Blood Flow



367359

Figure 5. Effect of CGRP Antagonist on Non-Human Primate Blood Pressure.



360/364

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/38799

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61P 25/06; A61K 31/535, 31/52, 31/55, 31/54, 31/495, 31/50; C07D 239/00, 243/10, 265/00, 285/00
US CL : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/11128 A1 (DR. KARL THOMAE G.M.B.H.) 19 March 1998, see Example No. 576, 580, 587, etc.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2004 (24.08.2004)	30 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Brenda Coleman Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

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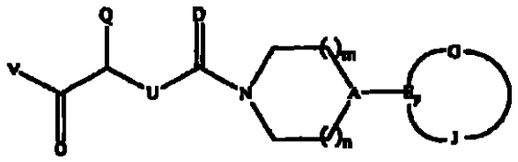
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(54) Título: ANTAGONISTA DEL RECEPTOR DE PEPTIDO RELACIONADO CON EL GEN DE CALCITONINA



(I)

(57) Resumen: La presente invención se refiere a compuestos de la Fórmula (I); como antagonistas de los receptores de péptidos relacionados con el gen de calcitonina ("receptor CGRP"), composiciones farmacéuticas que los comprenden, métodos para su identificación, métodos de tratamiento que los usan y su uso en terapia para tratamiento de la vasodilatación neurogénica, inflamación neurogénica, migraña, y otros dolores de cabeza, lesión térmica, choque circulatorio, sofocaciones asociadas con la menopausia, enfermedades inflamatorias de las vías respiratorias tales como asma y enfermedad pulmonar obstructiva crónica (COPD por sus siglas en inglés) y otras condiciones, el tratamiento de las cuales se puede efectuar por el antagonismo de los receptores CGRP.

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ANTAGONISTAS DEL RECEPTOR DE PEPTIDO RELACIONAD CON EL GEN DE CALCITONINA

Campo de la Invención

La presente invención se refiere a antagonistas novedosos de molécula pequeña de los receptores péptidos relacionados con el gen de calcitonina (receptor CGRP), composiciones farmacéuticas que los comprenden, métodos para su identificación, métodos de tratamiento que los usan y su uso en terapia para tratamiento de la vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza en racimo y otros dolores de cabeza, lesión térmica, choque circulatorio, sofocaciones asociadas con la menopausia, enfermedades inflamatorias de las vías aéreas tales como asma y enfermedad pulmonar obstructiva crónica (COPD por sus siglas en inglés) y otras condiciones, el tratamiento de las cuales se puede efectuar por el antagonismo de los receptores CGRP.

Antecedentes de la Invención

El péptido relacionado con el gen de calcitonina (CGRP) es un péptido que se presenta naturalmente de 37 aminoácidos identificado primero en 1982 (Amara, S.G. et al, *Science* 1982, 298, 240-244). Se expresan dos formas del péptido (αCGRP y βCGRP) que difieren por uno y tres aminoácidos en

las ratas y humanos respectivamente. El péptido se distribuye ampliamente en el sistema nervioso periférico (PNS por sus siglas en inglés) y el sistema nervioso central (CNS por sus siglas en inglés), localizado principalmente en las neuronas central y aferente sensorial, y despliega diversos efectos biológicos incluyendo la vasodilatación.

Cuando se libera de la célula, CGRP se enlaza a receptores acoplados con proteína G de superficie celular específica, y ejerce su acción biológica predominantemente por la activación de la adenilato ciclasa intracelular (Poyner, D. R. et al, Br J Pharmacol 1992, 105, 441-7; Van Valen, F. et al, Neurosci Lett 1990, 119, 195-8). Dos clases de receptores CGRP: $CGRP_1$ y $CGRP_2$, se han propuesto con base en las propiedades de antagonismo del fragmento del péptido CGRP(8-37) y la capacidad de los análogos lineales de CGRP para activar los receptores $CGRP_2$ (Juaneda, C. et al. *TiPS* 2000, 21, 432-438. Sin embargo, existe una falta de evidencia molecular para el receptor $CGRP_2$ (Brain, S. D. et al, *TiPS* 2002, 23, 51-53). El receptor $CGRP_1$ tiene tres componentes: (i) un receptor del tipo del receptor de calcitonina de la transmembrana 7 (CRLR); (ii) la proteína de tipo 1 que modifica la actividad del receptor de transmembrana sencilla (RAMP1) y (iii) la proteína del receptor intracelular (RCP)(Evans B, N, et al., *J. Biol Chem*, 2000, 275, 31438-43). RAMP1 se requiere para el transporte de CRLR a la membrana

del plasma y para el enlace del ligando para el receptor CGRP (McLatchie, L. M. et al, *Nature* 1998, 393, 333-339). El RCP se requiere para la transducción de señal (Evans B. N. et al., *J Biol Chem.* 2000, 275, 31438-43). Existen diferencias conocidas especificas de la especie en el enlace de antagonismo de molécula pequeña al receptor CGRP, con una afinidad típicamente mayor observada para el antagonismo del receptor humano que para otras especies (Brain, S. D. et al, *TiPS* 2000, 23, 51-53). La secuencia de aminoácidos RAMP1 determina la selectividad de la especie, en particular, el residuo de aminoácidos Trp74 es responsable del fenotipo del receptor humano (Mallee et al. *J Biol Chem* 2002, 277, 14294-8).

Se postulan los inhibidores al nivel del receptor para CGRP por ser útiles en condiciones patofisiológicas, en donde ha sucedido una activación excesiva del receptor CGRP. Algunos de estos incluyen vasodilatación neurogénica, inflamación neurogénica, migraña, dolor de cabeza en racimos y otros dolores de cabeza, lesiones térmicas, choque circulatorio, sofocaciones de la menopausia y asma. La activación del receptor CGRP ha estado implicada en la patogénesis del dolor de cabeza en migraña (Edvinsson L. *CNS Drugs* 2001;15(10):745-53; Williamson, D. J. *Microsc. Res. Tech.* 2001, 53, 167-178.; Grant, A. D. *Brit. J. Pharmacol.* 2002, 135, 356-362). Los niveles de suero de CGRP se elevan

durante la migraña (Goadsby PJ, et al. *Ann Neurol* 1990;28:183-7) y el tratamiento de fármacos contra migraña regresa los niveles CGRP a un coincidente normal con mejora del dolor de cabeza (Gallai V. et al. *Cephalalgia* 1995;15:384-90). Los que padecen migraña muestran niveles basales elevados de CGRP comparados a los controles (Ashina M, et al., Pain. 2000;86(1-2):133-8.2000). La infusión intravenosa CGRP produce un dolor de cabeza duradero en los que padecen migraña (Lassen LH, et al., *Cephalalgia*. 2002 Feb;22 (1): 54-61). Los estudios preclínicos en perros y ratas informan que el bloqueo sistémico CGRP con el antagonista de péptido CGRP(8-37), no altera la hemodinámica sistémica en reposo ni tampoco el flujo sanguíneo regional (Shen, Y-T. et al, *J Pharmacol Exp Ther* 2001, 298, 551-8). Así, los antagonistas del receptor CGRP pueden presentar un tratamiento novedoso para la migraña que evite los riesgos cardiovasculares de la vasoconstricción activa asociada con los agonistas no selectivos 5-$HT_{1B/1D}$, "triptanos" (por ejemplo sumatriptan).

Existen diversos modelos de migraña *in vivo* conocidos en la literatura (ver De Vries, P. et al, *Eur J Pharmacol* 1999,375,61-74). Algunos estimulan eléctricamente el ganglio trigémino y miden la dilatación de los vasos intracraneales que enervan (por ejemplo Williamson et al. *Cephalalgia* 1997 17:518-24). Ya que las arterias faciales también están

enervadas por el nervio trigémino, otros modelos estudian los cambios en el flujo sanguíneo facial inducido por la activación trigémina eléctrica (por ejemplo Escott et al. *Brain Res* 1995 669:93). Alternativamente, otros nervios periféricos (por ejemplo safenosos) y lechos vasculares (por ejemplo el fuljo sanguíneo abdominal) también se estudian (por ejemplo Escott al. *Br J Pharmacol* 1993 110, 772-6;). Todos los modelos se ha demostrado que se bloquean por el pretratamiento con el antagonista de péptidos CGPR(8-37), un fragmento de péptidos que está ausente de los primeros 7 residuos, o por un antagonista del receptor CGRP de molécula pequeña. En algunos casos, el CGRP exógeno se ha utilizado como un estímulo. Sin embargo, estos modelos son todos procedimientos terminales invasores, y ninguno ha demostrado el efecto abortivo clínicamente importante de revertir un incremento establecido en la dilatación arterial o un flujo sanguíneo creciente usando un tratamiento posterior de un antagonista del receptor CGRP. Williamson et al. *Cephalalgia* 1997 17:518-24 y Williamson et al. *Cephalalgia* 1997 17:525-31; utilizan inter alia entre otros CGRP intravenoso como un estímulo para incrementar el diámetro de la arteria dural intracraneal en ratas anestesiadas con pentobarbital de sodio, empleando un procedimiento terminal "intravital", que involucra perforar para adelgazar el cráneo y la creación de una ventana

craneal cerrada para visualizar las arterias durales. El efecto se bloquea por el pretratamiento con CGRP(8-37) intravenosamente. Escott et al, Brain Res 1995 669:93; entre otros, perforan dentro del cráneo de la rata y utilizan electrodos para el cerebro para estimular eléctricamente el ganglio trigémino y se mide el flujo sanguíneo facial Doppler con láser en un procedimiento terminal en ratas anestesiadas con pentobarbital de sodio que involucra un bloqueo neuromuscular, entubación de la tráquea y ventilación artificial. El efecto se bloquea por el pretratamiento con CGRP(8-37). Escott et al. *Br J Pharmacol* 1993 110, 772-6; *inter alia* utilizan CGRP intradérmico (i.d.) como el estímulo para incrementar el flujo sanguíneo en la piel abdominal de la rata, de animales anestesiados con pentobarbital de sodio, preparados con venas yugulares cánuladas para administración del fármaco y anestésico. Se bloqueó el efecto por el pretratamiento con i.v. CGRP (8-37). Chu et al. *Neurosci Lett* 2001 310, 169-72 usado *inter alia* CGRP intradermal como el estímulo en ratas y medidos los cambios Doppler con láser en el flujo sanguíneo en la piel de la espalda en un método terminal que utiliza pentobarbital de sodio en animales cánulados en la tráquea y anestesiados; y mostró un bloqueo de pretratamiento por la liberación continua de CGRP(8-37) a partir de bombas osmóticas implantadas subcutáneamente (s.c.). Hall et al *Br*

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J Pharmacol 1995 114, 592-7 y Hall et al *Br J Pharmacol* 1999 126, 280-4 *inter alia* usaron CGRP tópico para incrementar el diámetro de la arteria de la bolsa de la mejilla del hámster y CGRP intradermal para incrementar el flujo sanguíneo en la piel dorsal de rata de animales anestesiados con pentobarbital de sodio, preparados con venas yugulares cánuladas para la administración anestésica de fármaco. El efecto se bloquea por el pretratamiento con CGRP i.v. (8-37). Doods et al. Br J Pharmacol, 2000 Feb;129(3):420-3 *inter alia* perforado dentro del cráneo del titi (mono del nuevo mundo) y usaron electrodos para el cerebro para producir una estimulación eléctrica del ganglio trigémino y el flujo sanguíneo facial medido en un procedimiento terminal invasivo que involucra el bloque neuromuscular y la ventilación artificial de los primates anestesiados con pentobarbital de sodio. Se bloqueó el incremento del flujo por un pretratamiento del antagonista CGRP de molécula pequeña. Ver también WO 03/272252 Isolated DNA Molecules Encoding Humanized Calcitonin Gene-Related Peptide Receptor, Related Non-Human Transgenic Animals and Assay Methods. Así, el método de la presente invención en su procedimiento es, *inter alia,* un modelo de supervivencia no invasivo en primates que mide los cambios exógenos inducidos por CGRP en el flujo sanguíneo facial, y demuestra los efectos pre- y post-tratamiento de los antagonistas CGRP de molécula

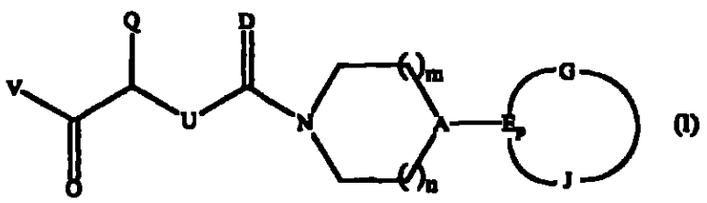
pequeña de péptidos en titíes anestesiados con isoflurano que respiran espontáneamente que se recuperan del procedimiento y que ofrece ventajas importantes.

Se han reportado recientemente diversos antagonistas del receptor CGRP de molécula pequeña que no son de péptido. WO 97/09046 y equivalentes describen *inter alia* compuestos de quinina y compuestos relacionados con la quinidina que son ligandos en particular del receptor CGRP. WO 98/09630 y WO 98/56779 y equivalentes describen *inter alia* diversos compuestos de nitrobenzamida como antagonistas del receptor CGRP. WO 01/32649, WO 01/49676 y WO 01/32648 y equivalentes describen *inter alia* una serie de 4-oxobutanamidas y derivados relacionados con el ciclopropano como antagonistas del receptor CGRP. WO 00/18764, WO 98/11128 y WO 00/55154 y equivalentes describen *inter alia* piperidinas de bencimidazolinilo como antagonistas del receptor CGRP. No relacionado con CGRP, se han descrito una serie de antagonistas de somatostatina en WO 99/52875 y WO 01/25228 y equivalentes. Ver también U.S. 6,344,449, U.S. 6,313,097, U.S. 6,521,609, U.S. 6,552,043, U.S. 20030181462, US20030191068 y WO 03/076432 y solicitudes relacionadas. Así, los antagonistas novedosos del receptor CGRP efectivos para el tratamiento de la inflamación neurogénica, migraña y otros trastornos serían ampliamente ventajosos.

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Breve Descripción de la Invención

Así de conformidad a una primera modalidad del primer aspecto de la invención se proporcionan compuestos de la Fórmula (I)



(I)

y sales farmacéuticamente aceptables y solvatos de los mismos

en donde

V es $-N(R^1)(R^2)$ o OR^4;

R^4 es H, alquilo C_{1-6}, haloalquilo C_{1-4}, o (alquileno C_{1-4})$_{0-1}R^{4'}$

$R^{4'}$ es cicloalquilo C_{3-7}, fenilo, adamantilo, quinuclidilo, azabiciclo[2.2.1]heptilo, azetidinilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino o dioxolanilo; y

$R^{4'}$ es opcionalmente substituido con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de halo, ciano, alquilo C_{1-4}, haloalquilo C_{1-4}, alcoxi C_{1-4}, hidroxi, amino, cicloalquilo C_{3-7}, alquilamino C_{1-3}, dialquilamino C_{1-3}, fenilo y bencilo; y

$R^{4'}$ opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de la estructura del anillo de $R^{4'}$;

R^1 y R^2 son cada uno independientemente L^1, en donde L^1 se selecciona del grupo que consiste de H, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, -alquileno C_{1-6}-amino(alquilo C_{1-3})$_2$, cicloalquilo C_{3-7}, fenilo, azetidinilo, adamantilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino y dioxolanilo; y

R^1 y R^2 son cada uno opcionalmente e independientemente substituidos con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de halo, ciano, alquilo C_{1-4}, haloalquilo C_{1-4}, alcoxi C_{1-4}, hidroxi, amino, cicloalquilo C_{3-7}, alquilamino

C_{1-3}, dialquilamino C_{1-3}, (alquilo C_{1-3})$_{0-2}$ureido, fenilo y bencilo;

R^1 y R^2 opcionalmente e independientemente contienen 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los heterociclos que comprenden R^1 y R^2;

en donde L^1 es opcionalmente e independientemente interrumpida del nitrógeno al cual esto se enlaza por L^2, en donde L^2 es independientemente alquileno C_{1-3} o alquilideno C_{1-3}; o

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es opcionalmente substituido con Y, en donde Y es dioxolanilo, alquilo C_{1-9}, alquenilo C_{2-9}, alcoxi C_{2-4}, cicloalquilo C_{3-7}, fenilo, azetidinilo, furanilo, tienilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobenzimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, benzisotiazolilo o tiomorfolino;

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y en donde X e Y son opcionalmente interrumpidos con Z, en donde Z es -NHC(O)O-, -NHC(O)NH-, -NC(O)NH_2, -NH-, alquileno C_{1-3}, alquileno C_{1-3}, alquenileno-C_{1-3}-NHC(O)O-alquileno C_{1-3}; y opcionalmente e independientemente substituidos con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de alquilo C_{1-4}, amino, alquilamino C_{1-3}, -alquileno C_{1-6}-amino(alquilo C_{1-3})$_2$, (alquilo C_{1-3})$_{0-2}$ureido, fenilo y bencilo;

X e Y opcionalmente e independientemente contienen 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los heterociclos que comprenden X e Y;

con la condición de que si X es substituido con Y, y si X e Y no se interrumpen con Z, luego X e Y opcionalmente comparten un átomo de carbono y juntos forman una porción espirocíclica;

Q es Q' ó Q";

en donde Q' es $NH(S^y)_sR^3$; y

Q" es $NH(S^y)_sR^3$, $NHC(O)(S^y)_sR^3$, $NHC(O)O(S^y)_sR^3$, $NHC(O)NH(S^y)_sR^3$, $O(S^y)_sR^3$, $(S^y)_sNHR^3$, $(S^y)_sNHC(O)R^3$, $(S^y)_sNHC(O)OR^3$, $(S^y)_sNHC(O)NHR^3$ o $(S^y)_sOR^3$;

en donde S^y es alquileno C_{1-3} o alquilideno C_{1-3} y s es 0 ó 1;

U es CH_2 o NH;

con la condición de que si Q es Q", luego U es CH_2;

R^3 es R^{3a} o R^{3b}

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en donde

R^{3a} es

(i) un heterociclo que tiene dos anillos fusionados con 5 hasta 7 miembros en cada uno de los anillos, el heterociclo que contiene uno hasta cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los anillos fusionados;

(ii) un heterociclo de 4 hasta 6 miembros que contiene uno hasta tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S, opcionalmente contienen 1 hasta 2 carbonilos, en donde el átomo de carbono de carbonilo es un miembro del heterociclo de 4 hasta 6 miembros;

(iii) cicloalquilo C_{3-7};

(iv) carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquileno C_{1-4}-fenilo o naftilo; o

(v) alquilo C_{1-8}, alquenilo C_{2-7}, $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo C_{2-7}; y

en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquenilfenilo C_{1-3},-alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, alquilo C_{1-6}, mono-bi-tri-haloalquilo C_{1-3}, mono-

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bi-tri-haloalquiloxi C_{1-3}, (alquilo C_{1-3})$_{1-2}$amina, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$;

$R^{3'}$ es H o alquilo $-C_{1-6}$;

con la condición de que si R^{3a} es $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, ó $-C(O)O-R^{3'}$, luego el $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ ó $-C(O)O-R^{3'}$ no son substituidos;

R^{3b} es R^{3a} pero no es fenilo, 1-naftilo, 2-naftilo, 1,2,3,4-tetrahidro-1-naftilo, 1H-indol-3-ilo, 1-metil-1H-indol-3-ilo, 1-formil-1H-indol-3-ilo, dimetiletoxicarbonil)-1H-indol-3-ilo, 4-imidazolilo, 1-metil-4-imidazolilo, 2-tienilo, 3-tienilo, tiazolilo, 1H-indazo-3-ilo, 1-metil-1H-indazol-3-ilo, benzo[b]fur-3-ilo, benzo[b]tien-3-ilo, piridinilo, quinolinilo o isoquinolinilo; opcionalmente substituido en el esqueleto de carbono con mono-, di- o trisubstituido por átomos de flúor, cloro o bromo o por grupos alquilo ramificados o no ramificados, grupos cicloalquilo C_{3-8}, grupos fenilalquilo, grupos alquenilo, alcoxi, fenilo, fenilalcoxi, trifluorometilo, alcoxicarbonilalquilo, carboxialquilo, alcoxicarbonilo, carboxi, dialquilaminoalquilo, dialquilaminoalcoxi, hidroxi, nitro, amino, acetilamino, propionilamino, benzoilo, benzoilamino, benzoilmetilamino, metilsulfoniloxi, aminocarbonilo, alquilaminocarbonilo,

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dialquilaminocarbonilo, alcanoilo, ciano, tetrazolilo, fenilo, piridinilo, tiazolilo, trifluorometoxi, trifluorometiltio, trifluorometilsulfinilo o trifluorometilsulfonilo;

en donde los substituyentes pueden ser el mismo o diferente y los grupos benzoilo mencionados arriba, benzoilamino y benzoilmetilamino pueden adicionalmente volverse a sustituir en la porción fenilo por un átomo de flúor, cloro o bromo, o por un grupo alquilo, trifluorometilo, amino o acetilamino;

D es O, NCN o alquilo NSO_2C_{1-3};

A es C, N o CH;

m y n son independientemente 0, 1 ó 2;

con la condición de que

si m y n son 0, luego A no es N;

si m es 2, luego n no es 2; o

si n es 2, luego m no es 2;

E es N, CH o C;

p es 0 ó 1;

si p es 1, luego G, J y E juntos forman A^x o A^y;

A^x es un heterociclo fusionado que tiene dos anillos fusionados con 5 hasta 7 miembros en cada uno de los anillos, el heterociclo contiene uno hasta cuatro de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S; y opcionalmente contiene 1 ó 2 carbonilos en

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donde el átomo de carbono de carbonilo es un miembro del heterociclo fusionado;

A^y es un heterociclo de 4 hasta 6 miembros que contienen uno hasta tres heteroátomos seleccionados del grupo que consiste de N y S; y opcionalmente contiene 1 hasta 2 carbonilos, en donde el átomo de carbono de carbonilo es un miembro del heterociclo de 4 hasta 6 miembros;

en donde A^x y A^y son opcionalmente substituidos con alquilo C_{1-4}, alcoxi C_{1-4}, haloalquilo C_{1-4}, ciano, cicloalquilo C_{3-7}, fenilo, halofenilo, halo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; o

si p es 0 tal que G y J se enlazan a A, luego A es C, y G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA' o GJA";

en donde

GJA' es A^x o A^y; y

GJA" es A^x o A^y;

con la condición de que

A^x no es un heterociclo 1,3-diaza-fusionado; y

A^y no es un 1,3-diaza-heterociclo;

y además con la condición de que si Q es Q", luego R^3 es R^{3a}; y

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si Q es Q', luego

R^3 es R^{3b}; o

R^3 es R^{3a}, p es 0 y G, J y A juntos forman GJA".

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y R^3 es R^{3b}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', R^3 es R^{3a} y p es 0 tal que G, J y A juntos forman GJA".

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y Q' es $(S^y)_sR^3$ y s es 0.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y Q' es $(S^y)_sR^3$, S^y es alquileno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y Q' es $(S^y)_sR^3$, S^y es alquilideno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y U es CH_2.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, s es 0 y U es CH_2.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, S^y es alquileno C_{1-3}, s es 1 y U es CH_2.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, S^y es alquilideno C_{1-3}, s es 1 y U es CH_2.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y U es NH.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la

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presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, s es y U es NH.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, S^y es alquileno C_{1-3}, s es 1 y U es NH.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q', Q' es $(S^y)_sR^3$, R^3, S^y es alquilideno C_{1-3}, s es 1 y U es NH.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q".

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NH(S^y)_sR^3$.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NH(S^y)_sR^3$ y s es 0.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NH(S^y)_sR^3$, S^y es alquileno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NH(S^y)_sR^3$, S^y es alquilideno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)(S^y)_sR^3$.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)(S^y)_sR^3$ y s es 0.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)(S^y)_sR^3$, S^y es alquileno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad

a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)(S^y)_sR^3$, S^y es alquilideno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)O(S^y)_sR^3$.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)O(S^y)_sR^3$ y s es 0.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)O(S^y)_sR^3$, S^y es alquileno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)O(S^y)_sR^3$, S^y es alquilideno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)NH(S^y)_sR^3$.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)NH(S^y)_sR^3$ y s es 0.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)NH(S^y)_sR^3$, S^y es alquileno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y Q" es $NHC(O)NH(S^y)_sR^3$, S^y es alquilideno C_{1-3} y s es 1.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es OR^4.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es OR^4 y R^4 es alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad

a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde

V es $-N(R^1)(R^2)$ o OR^4;

R^4 es H, alquilo C_{1-6}, Haloalquilo C_{1-4}, (alquileno C_{1-4})$_{0-1}R^{4'}$

$R^{4'}$ es cicloalquilo C_{3-7}, fenilo, adamantilo, quinuclidilo, azabiciclo[2.2.1]heptilo, azetidinilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino o dioxolanilo; y

$R^{4'}$ es opcionalmente substituido con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de halo, ciano, alquilo C_{1-4}, haloalquilo C_{1-4}, alcoxi C_{1-4}, hidroxi, amino, dialquilamino C_{3-7}, alquilamino C_{1-3}, dialquilamino C_{1-3}, (alquilo C_{1-3})$_{0-2}$ureido, fenilo y bencilo;

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$R^{4'}$ opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de la estructura del anillo de $R^{4'}$;

R^1 y R^2 son cada uno independientemente L^1, en donde L^1 selecciona del grupo que consiste de H, alquilo C_{1-6}, -alquileno C_{1-6}-amino(alquilo C_{1-3})$_2$, cicloalquilo C_{3-7}, fenilo, adamantilo, azetidinilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino y dioxolanilo; y

R^1 y R^2 son cada uno opcionalmente e independientemente substituidos con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de halo, ciano, alquilo C_{1-4}, haloalquilo C_{1-4}, alcoxi C_{1-4}, hidroxi, amino, cicloalquilo C_{3-7}, alquilamino C_{1-3}, dialquilamino C_{1-3}, (alquilo C_{1-3})$_{0-2}$ureido, fenilo y bencilo;

R^1 y R^2 opcionalmente e independientemente contienen 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los heterociclos que comprenden R^1 y R^2;

en donde L^1 es opcionalmente interrumpido a partir del

nitrógeno al cual esto se enlaza por L^2, en donde L^2 es alquileno C_{1-3}; o

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es azetidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es opcionalmente substituido con Y, en donde Y es dioxolanilo, alquilo C_{1-4}, alquilamino C_{1-4}, dialquilamino C_{1-4}, alcoxi C_{1-4}, cicloalquilo C_{3-7}, fenilo, azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobenzimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, benzisotiazolilo o tiomorfolino; y en donde X e Y son opcionalmente interrumpidos con Z, en donde Z es -NHC(O)O-, -NHC(O)NH-, NC(O)NH_2, -NH-, alquileno C_{1-3}, alquileno C_{1-3}, NHC(O)O-alquileno C_{1-3}, y opcionalmente e independientemente substituidos con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de alquilo C_{1-4}, amino, alquilamino C_{1-3}, alquileno C_{1-6}-amino(alquilo C_{1-3})$_2$, (alquilo C_{1-3})$_{0-2}$ ureido, fenilo y bencilo;

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X e Y opcionalmente e independientemente contienen 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los heterociclos que comprenden X e Y; con la condición de que si X es substituido con Y, y si X e Y no se interrumpen con Z, luego X e Y opcionalmente comparten un átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^4 es H, alquilo C_{1-6}, haloalquilo C_{1-4} o (alquileno C_{1-4})$_{0-1}R^{4'}$; $R^{4'}$ es cicloalquilo C_{3-7}, fenilo, adamantilo, quinuclidilo, azabiciclo[2.2.1]heptilo, azetidinilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino o dioxolanilo; y $R^{4'}$ es opcionalmente substituido con 1 ó 2 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de halo, ciano, alquilo C_{1-4}, haloalquilo C_{1-4}, alcoxi C_{1-4}, hidroxi, amino, cicloalquilo C_{3-7}, fenilo y bencilo.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^4 es H, alquilo C_{1-4}, haloalquilo C_{1-4} o (alquileno C_{1-4})$_{0-1}R^{4'}$; $R^{4'}$ cicloalquilo C_{3-7}, fenilo, adamantilo, quinuclidilo, azabiciclo[2.2.1]heptilo, azetidinilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino o dioxolanilo.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^4 es H, alquilo C_{1-6} o (alquileno C_{1-4})$_{0-1}R^{4'}$; $R^{4'}$ es cicloalquilo C_{3-7}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y

R^1 y R^2 son cada uno independientemente L^1, en donde L^1 selecciona del grupo que consiste de H, alquilo C1-6, -

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alquileno C_{1-6}-amino(alquilo C_{1-3})$_2$, cicloalquilo C_{3-7}, fenilo, azetidinilo, adamantilo, tetrahidrofuranilo, furanilo, dioxolanilo, tienilo, tetrahidrotienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, piranilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, piperidinilo, piperazinilo, morfolino, tiomorfolino y dioxolanilo; o

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es azetidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piperazinilo, piperidinilo, morfolino o tiomorfolino;

en donde X es substituido con Y, en donde Y es dioxolanilo, alquilo C_{1-4}, alcoxi C_{1-4}, cicloalquilo C_{3-7}, fenilo, azetidinilo, pirrolilo, pirrolinilo, pirrolidinilo, pirrolidinonilo, imidazolilo, imidazolinilo, imidazolidinilo, imidazolidinonilo, pirazolilo, pirazolinilo, pirazolidinilo, azepinilo, diazepinilo, piridilo, pirimidinilo, dihidrobenzimidazolonilo, piperazinilo, piperidinilo, morfolino, benzotiazolilo, benzisotiazolilo o tiomorfolino;

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y en donde X e Y opcionalmente comparten un átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y

R^1 y R^2 son cada uno independientemente L^1, en donde L^1 se selecciona del grupo que consiste de H, alquilo C_{1-6}, o

R^1 y R^2 junto con el nitrógeno al cual se enlazan forman X,

en donde X es piperidinilo o morfolino;

en donde X es substituido con Y, en donde Y es dioxolanilo, alquilo C_{1-4} o piperidinilo;

y en donde X e Y opcionalmente comparten un átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde R^1 y R^2 son cada uno independientemente L^1, en donde L^1 selecciona del grupo que consiste de H, alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde

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R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es piperidinilo o morfolino;

en donde X es substituido con Y, en donde Y es dioxolanilo, alquilo C_{1-4} o piperidinilo;

y en donde X e Y opcionalmente comparten un átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es piperidinilo;

en donde X es substituido con Y, en donde Y es piperidinilo.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es morfolino;

en donde X es substituido con Y, en donde Y es alquilo C_{1-4}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es piperidinilo;

en donde X es substituido con Y, en donde Y es alquilo C_{1-4}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde V es $-N(R^1)(R^2)$ y en donde

R^1 y R^2 junto con el nitrógeno al cual se enlazan a partir de X,

en donde X es piperidinilo;

en donde X es substituido con Y, en donde Y es dioxolanilo;

y en donde X e Y se dividieron en átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde X e Y no se interrumpen con Z.

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De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde X e Y no se interrumpen con Z; y X e Y se dividieron en átomo de carbono y juntos forman una porción espirocíclica.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde es R^3 es R^{3a}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es un heterociclo que tiene dos anillos fusionados con 5 hasta 7 miembros en cada uno de los anillos, el heterociclo que contiene uno hasta cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente

invención en donde R^{3a} es un heterociclo que tiene dos anillos fusionados con 5 hasta 7 miembros en cada uno de los anillos, el heterociclo que contiene uno hasta cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los anillos fusionados.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es un heterociclo que tiene dos anillos fusionados con 5 hasta 7 miembros en cada uno de los anillos, el heterociclo que contiene uno hasta cinco de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S y el heterociclo opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono de carbonilo es un miembro de los anillos fusionados; en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo C_{1-3}, -alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo C_{1-3}, mono-bi-tri-haloalquiloxi C_{1-3}, alcoxi C_{1-6}, (alquilo C_{1-3})$_{1-2}$amina, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, -

$N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$; $R^{3'}$ es H o alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es un heterociclo de 4 hasta 6 miembros que contiene uno hasta tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es un heterociclo de 4 hasta 6 miembros que contiene uno hasta tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y S, opcionalmente contiene 1 hasta 2 carbonilos, en donde el átomo de carbono de carbonilo es un miembro del heterociclo de 4 hasta 6 miembros.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es un heterociclo de 4 hasta 6 miembros que contiene uno hasta tres de los mismos o diferentes heteroátomos seleccionados del grupo que consiste de O, N y

S, opcionalmente contiene 1 hasta 2 carbonilos, en donde el átomo de carbono de carbonilo es un miembro del heterociclo de 4 hasta 6 miembros; en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo C_{1-3}, -alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo C_{1-3}, mono-bi-tri-haloalquiloxi C_{1-3}, alcoxi C_{1-6}, (alquilo C_{1-3})$_{1-2}$amina, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$; $R^{3'}$ es H o alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es cicloalquilo C_{3-7}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es cicloalquilo C_{3-7}; en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo C_{1-3}, -alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo C_{1-3}, mono-bi-tri-haloalquiloxi C_{1-3}, alcoxi

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C_{1-6}, (alquilo $C_{1-3})_{1-2}$amina, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$; $R^{3'}$ es H o alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es carbazolilo, fluorenilo, -O-fenilo, -O-alquileno C_{1-4}-fenilo, o naftilo.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es carbazolilo, fluorenilo, fenilo, -O-fenilo, -O-alquileno C_{1-4}-fenilo, o naftilo; en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo C_{1-3}, -alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo C_{1-3}, mono-bi-tri-haloalquiloxi C_{1-3}, alcoxi C_{1-6}, (alquilo $C_{1-3})_{1-2}$amina, $-OR^{3'}$, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $N(R^{3'})C(O)(R^{3'})_2$, $-N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$; $R^{3'}$ es H o -alquilo C_{1-6}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad

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a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es alquilo C_{1-8}, alquenilo C_{2-7}, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo C_{2-7}.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^{3a} es alquilo C_{1-8}, alquenilo C_{2-7}, $-C(O)R^{3'}$, $-C(O)O-R^{3'}$ o alquinilo C_{2-7}; en donde R^{3a} es opcionalmente substituido con 1 hasta 3 de los mismos o diferentes substituyentes seleccionados del grupo que consiste de bencilo, fenilo, -O-fenilo, -O-alquilfenilo C_{1-3}, -alquileno C_{1-3}-OC(O)-fenilo, ciano, amino, nitro, halo, mono-bi-tri-haloalquilo C_{1-3}, mono-bi-tri-haloalcoxi C_{1-3}, alcoxi C_{1-6}, (alquilo C_{1-3})$_{1-2}$amina, $-OR^{3'}$, $C(O)R^{3'}$, $-C(O)O-R^{3'}$, $-O-C(O)R^{3'}$, $-N(R^{3'})_2$, $-C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)(R^{3'})_2$, $N(R^{3'})C(O)N(R^{3'})_2$, $-N(R^{3'})C(O)OR^{3'}$, $-O-C(O)N(R^{3'})_2$, $-N(R^{3'})SO_2R^{3'}$, $-SO_2N(R^{3'})_2$ y $-SO_2R^{3'}$; $R^{3'}$ es H o alquilo C_{1-6}; con la condición de que si R^{3a} es $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$, o $-C(O)O-R^{3'}$, luego $-C(O)R^{3'}$, $CHC(O)O-R^{3'}$, $CH(CH_3)C(O)O-R^{3'}$ o $-C(O)O-R^{3'}$ no son substituidos.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3a} y R^{3a} es fenilo, hidroxifenilo, azetidinilo, naftilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo

C_{2-6}, dihidroquinolinonilo, hidroquinolinonilo, quinolinilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, isoquinolinilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, benzimidazolilo, indazolilo, dihidrobenzimidazolonilo, hidrobenzimidazolonilo, benzimidazolinilo, dihidro-benztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzoxazolilo, benzotriazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, benzotienilo, dihidrobenzofuranonilo, dihidroindolonilo, hidroindolonilo, indolilo, indolizinilo, isoindolilo, indolinilo, indazolilo, pirazolilo, pirazolinilo, pirazolidinilo, furanilo, tienilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, piridilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, triazolopirimidinilo, tetrahidropirazolopiridinilo, piperazinilo o morfolino; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3a} y R^{3a} es fenilo, naftilo, indazolilo, benzimidazolinilo, dihidrobenzoxazolilo, benzotriazolilo, benzotienilo, benzdioxolanilo,

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dihidroindolonilo, indolilo, furanilo, tienilo, piridilo, purinilo, carbazolilo, piperidinilo, triazolopirimidinilo, tetrahidropirazolopiridinilo; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3a} y R^{3a} es dihidro-benztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, benzotienilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzofuranilo, dihidroindolonilo, hidroindolonilo, indolilo, indolizinilo, isoindolilo, indolinilo o indazolilo; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3a} y R^{3a} es dihidrobenzoxazolilo, benzotriazolilo, indolilo, halonitrofenilo, halopirimidina, halopurinilo, alquilo C_{1-3}-nitroaminopirimidina, triazolopirimidinilo, piridilo, indazolilo, fenilo o benzdioxolanilo; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

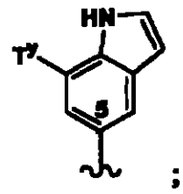
De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad

a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3a} y R^{3a} es naftilo, fenilo-O-fenilo, o tienilo; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b}.

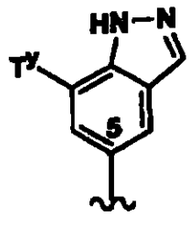
De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es

1H-Indazol-5-ilo



;

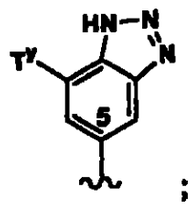
1H-Indazol-5-ilo



;

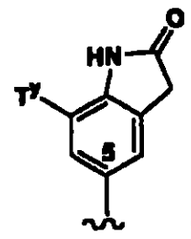
1H-Benzotriazol-5-ilo

HS 402



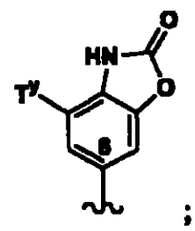
;

1,3-Dihidro-indol-2-on-5-ilo



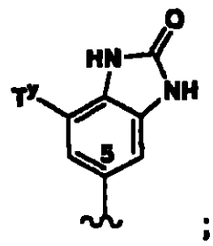
;

3H-Benzooxazol-2-on-6-ilo



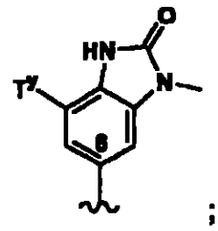
;

1,3-Dihidro-benzoimidazol-2-on-5-ilo



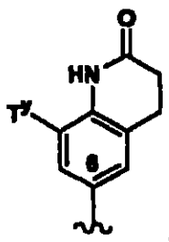
;

1-Metil-1,3-dihidro-benzimidazol-2-on-6-ilo



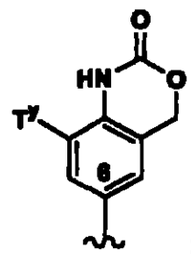
;

3,4-Dihidro-1H-quinolin-2-on-6-ilo



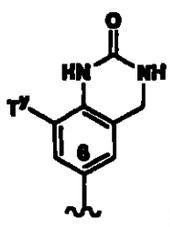
;

1,4-Dihidro-benzo[d][1,3]oxazin-2-on-6-ilo



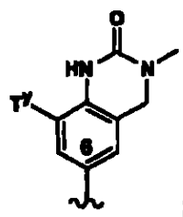
;

3,4-Dihidro-1H-quinazolin-2-on-6-ilo



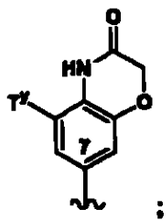
;

3-Metil-3,4-dihidro-1H-quinazolin-2-on-6-ilo



;o

4H-Benzo[1,4]oxazin-3-on-7-ilo



;

en donde T^y es H, alquilo C_{1-4}, F, Cl, Br o nitrilo.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es azetidinilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, benzimidazolilo, 1H-indazol-5-ilo, dihidrobenzimidazolonilo, hidrobenzimidazolonilo, benzimidazolinilo, dihidro-benztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo,

dihidrobenzofuranonilo, hidrobenzofuranonilo, benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, dihidroindolonilo, hidroindolonilo, indolizinilo, isoindolilo, indolinilo, pirazolilo, pirazolinilo, pirazolidinilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es dihidrobenzimidazolonilo, hidrobenzimidazolonilo, benzimidazolinilo, dihidro-benztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, 1H-indazol-5-ilo, benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, dihidroindolonilo, hidroindolonilo, indolizinilo, isoindolilo, indolinilo, pirazolilo, pirazolinilo, pirazolidinilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

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De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es azetidinilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, dihidroquinazolinonilo, hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, benzimidazolilo, 1H-indazol-5-ilo, dihidrobenzimidazolonilo, hidrobenzimidazolonilo, benzimidazolinilo, dihidro-benztiazolonilo, hidrobenztiazolonilo, benztiazolilo, dihidrobenzotiofenonilo, hidrobenzotiofenonilo, dihidrobenzofuranonilo, hidrobenzofuranonilo, benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es azetidinilo, alquilo C_{1-6}, alquenilo C_{2-6}, alquinilo C_{2-6}, dihidroquinolinonilo, hidroquinolinonilo, dihidroisoquinolinonilo, hidroisoquinolinonilo, dihidroquinazolinonilo,

hidroquinazolinonilo, quinazolinilo, dihidroquinoxalinonilo, hidroquinoxalinonilo, quinoxalinilo, benzimidazolilo, benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, dihidroindolonilo, hidroindolonilo, 1H-indazol-5-ilo, indolizinilo, isoindolilo, indolinilo, pirazolilo, pirazolinilo, pirazolidinilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, purinilo, carbazolilo, pirimidinilo, piperidinilo, piperazinilo o morfolino; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es benzdioxolanilo, dihidrobenzoxazolilo, benzotriazolilo, purinilo, carbazolil; opcionalmente substituido como se proporciona en la primera modalidad del primer aspecto.

De conformidad a otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad a la primera modalidad del primer aspecto de la presente invención en donde R^3 es R^{3b} y R^{3b} es dihidrobenzoxazolilo, benzotriazolilo, indolilo, halonitrofenilo, halopirimidinilo, halopurinilo, alquilo C_{1-3}-nitroaminopirimidinilo, triazolopirimidinilo, piridilo, 1H-indazol-5-ilo, fenilo o benzdioxolanilo.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y en donde los compuestos tienen una configuración absoluta de R.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde Q es Q' y en donde los compuestos tiene una configuración absoluta de S.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y en donde los compuestos tienen una configuración absoluta de R.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde Q es Q" y en donde los compuestos tiene una configuración absoluta de S.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde m y n son cada uno 1.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde D es O.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A es C.

De conformidad con otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A es CH.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A es N.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde E es N.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde E es CH.

De conformidad con otra modalidad del primer aspecto de

la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde E es C.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde los compuestos exhiben como se describe aquí un enlace CGRP IC_{50} de menos de 10 nM.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde los compuestos exhiben como se describe aquí un enlace CGRP IC_{50} de menos de 100 nM.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde los compuestos exhiben como se describe aquí un enlace CGRP IC_{50} de menos de 1000 nM.

De conformidad con otra modalidad el primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 1; y G, J y E juntos forman A^x o A^y.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de

conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 1; y G, J y E juntos forman A^x.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 1; y G, J y E juntos forman A^y.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^x es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos, el heterociclo contiene uno a cuatro heteroátomos iguales o diferentes seleccionados del grupo que consiste de O, N y S; y opcionalmente contiene 1 ó 2 carbonilos en donde el átomo de carbono del carbonilo es un miembro del heterociclo fusionado.

De conformidad con otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^x es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos el heterociclo contiene uno a cuatro heteroátomos iguales o diferentes seleccionados del grupo que consiste de O, N y S.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención, en donde A^x es un heterociclo que tiene dos anillos fusionados con 5 a 7 miembros en cada uno de los anillos el heterociclo contiene uno a cuatro heteroátomos iguales o diferentes seleccionados del grupo que consiste de 0, N y S y en donde A^x está substituido con fenilo.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^x es un heterociclo fusionado descrito en la presente.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^y es un heterociclo de 4 a 6 miembros que contiene uno a tres heteroátomos seleccionados del grupo que consiste de 0, N y S; y opcionalmente contiene 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un heterociclo de 4 a 6 miembros.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^y es un heterociclo de 4 a 6

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miembros que contiene uno a tres heteroátomos seleccionados del grupo que consiste de O, N y S.

De conformidad con otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención, en donde A^y es un heterociclo de 4 a 6 miembros que contiene uno a tres heteroátomos seleccionados del grupo que consiste de 0, N y S; y opcionalmente contiene 1 a 2 carbonilos, en donde el átomo de carbono del carbonilo es un miembro de 4 a 6 miembros heterociclos; y en donde A^y es substituido con fenilo.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde A^y es un heterociclo de 4 a 6 miembros descritos en la presente.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada que se coloca a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA' o GJA".

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de

conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA'.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocado a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contienen A y en donde G, J y A juntos son GJA".

De conformidad con otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA' y GJA' es A^x.

De conformidad con otra modalidad del primer aspecto de la presente invención se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del

sistema que contiene A y en donde G, J y A juntos son GJA' y GJA' es A^y.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA" y GJA" es A^x.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son GJA" y GJA" es A^y.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos forman un heterociclo seleccionados del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo,

dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo, dihidrobenzoxazinonilo, dihidrobencimidazolonilo, dihidrobencimidazolilo, dihidrobenztiazolonilo, dihidrobenztiazolilo, dihidrobenzotiofenonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinil y morfolino; en donde el heterociclo es opcionalmente substituido con C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}haloalquilo, ciano, C_{3-7}cicloalquilo, fenilo, halofenilo, furanilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinil o morfolino.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son forman un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo,

dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo, dihidrobenzoxazinonilo, dihidrobenzimidazolonilo, dihidrobencimidazolilo, dihidrobenztiazolonilo, dihidrobenztiazolilo, dihidrobenzotiofenonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinil y morfolino; en donde el heterociclo es opcionalmente substituido con C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}haloalquilo, ciano, C_{3-7}cicloalquilo, fenilo, halofenilo, furanilo, pirazolilo, pirazolinilo, pirazolidinilo, piridilo, pirimidinilo, piperidinilo, piperazinil o morfolino.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos son forman un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo,

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imidazolinilo, imidazolidinilo, piperidinilo, piperazinilo y morfolino; en donde el heterociclo es opcionalmente substituido con C_{1-4}alquilo, C_{1-4}alcoxi, C_{1-4}haloalquilo, ciano, C_{3-7}cicloalquilo, fenilo, halofenilo, piperazinilo o morfolino.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos forman un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo, dihidrobenzoxazinonilo, dihidrobenzimidazolonilo, dihidrobenzimidazolilo, dihidrobenztiazolonilo, dihidrobenztiazolilo, dihidrobenzotiofenonilo, dihidrobenzofuranonilo, dihidroindolonilo, indolinilo, pirazolinilo, pirazolidinilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, piperidinilo, piperazinil y morfolino.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de

conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos forman un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonilo, dihidrobenzoxazinilo, hidrobenzoxazinilo y dihidrobenzoxazinonilo.

De conformidad con otra modalidad del primer aspecto de la presente invención, se proporcionan compuestos de conformidad con la primera modalidad del primer aspecto de la presente invención en donde p es 0 tal que G y J son cada uno colocados a A, entonces G, J y A juntos forman un sistema de anillo espirocíclico con los anillos del sistema que contiene A y en donde G, J y A juntos forman un heterociclo seleccionado del grupo que consiste de imidazolinonilo, imidazolidinonilo, dihidroquinolinonilo, dihidroisoquinolinonilo, dihidroquinazolinonilo, dihidroquinoxalinonil y dihidrobenzoxazinilo.

De conformidad con varias modalidades de un segundo aspecto de la presente invención se proporcionan composiciones farmacéuticas que comprenden compuestos de la fórmula (I) como se define en la presente.

De conformidad con varias modalidades del tercer aspecto de la presente invención se proporcionan métodos de tratamiento inflamatorio (particularmente inflamación neurogenica), dolor de cabeza (particularmente migraña), dolor, lesión térmica, choque ciruculatorio, diabetes, síndrome de Reynaud, insuficiencia arterial periférica, hemorragia subaracnoide/craneal, crecimiento de tumores, sofocaciones asociadas con la menopausia y otras condiciones, el tratamiento de las cuales se puede efectuar por el antagonismo del receptor CGRP por la administración de composiciones farmacéuticas que comprenden los compuestos de la Fórmula (I) como se define en la presente.

De conformidad con varias modalidades de un cuarto aspecto de la presente invención con usos de los compuestos de la presente invención seleccionados del grupo que consiste de (a) regulación inmune en la mucosa de la gota; (b) efecto protector contra la lesión cardiaca anafiláctica; (c) estimulación o prevención de la estimulación de la interleucina-1b(IL-1b) de la resorción del hueso; (d) modulación de la expresión de los receptores NK1 en neuronas espinales y (e) enfermedades inflamatorias de las vías aéreas y enfermedad pulmonar obstructiva crónica incluyendo asma. Ver (a) Calcitonin Receptor-Like Receptor Is Expressed on Gastrointestinal Immune Cells. Hagner, Stefanie; Knauer, Jens; Haberberger, Rainer; Goeke, Burkhard; Voigt, Karlheinz;

McGregor, Gerard Patrick. Institute of Physiology, Philipps University, Marburg, Alemania. Digestion (2002), 66(4), 197-203; *(b)* Protective effects of calcitonin gene-related peptide-mediated evodiamine on guinea-pig cardiac anaphylaxis. Rang, Wei-Qing; Du, Yan-Hua; Hu, Chang-Ping; Ye, Feng; Tan, Gui-Shan; Deng, Han-Wu; Li, Yuan-Jian. School of Pharmaceutical Sciences, Department of Pharmacology, Central South University, Xiang-Ya Road 88, Changsha, Hunan, Naunyn-Schmiedeberg's Archives of Pharmacology (2003), 367(3),306-311; *(c)* The experimental study on the effect calcitonin gene-related peptide on bone resorption mediated by interleukin-1. Lian, Kai; Du, Jingyuan; Rao, Zhenyu; Luo, Huaican. Department of Orthopedics, Xiehe Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, República Popular de China. Journal of Tongj y Medical University (2001), 21(4), 304-307, *(d)* Calcitonin gene-related Peptide regulates expression of neurokinin 1 receptors by rat spinal neurons. Seybold VS, McCarson KE, Mermelstein PG, Groth RD, Abrahams LG. J. Neurosci. 2003 23 (5): 1816-1824. Department of Neuroscience, University of Minnesota, Minneapolis, Minnesota 55455, and Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, Kansas 66160 *(e)* Attenuation of antigen-induced airway hyperresponsiveness in CGRP-deficient mice. Aoki-Nagase,

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Tomoko; Nagase, Takahide; Oh-Hashi, Yoshio; Shindo, Takayuki; Kurihara, Yukiko; Yamaguchi, Yasuhiro; Yamamoto, Hiroshi; Tomita, Tetsuji; Ohga, Eijiro; Nagai, Ryozo; Kurihara, Hiroki; Ouchi, Yasuyoshi. Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokio, Japón. American Journal of Physiology (2002), 283(5,Pt. 1), L963 L970; *(f)* Calcitonin gene-related peptide as inflammatory mediator. Springer, Jochen; Geppetti, Pierangelo; Fischer, Axel; Groneberg, David A. Charite Campus Virchow, Department of Pediatric Pneumology and Immunology, Division of Allergy Research, Humboldt-University Berlin, Berlín, Alemania. Pulmonary Pharmacology & Therapeutics (2003), 16(3), 121-130; y *(g)* Pharmacological targets for the inhibition of neurogenic inflammation. Helyes, Zsuzsanna; Pinter, Erika; Nemeth, Jozsef; Szolcsanyi, Janos. Department of Pharmacology y Pharmacotherapy, Faculty of Medicine, University of Pecs, Pecs, Hung. Current Medicinal Chemistry: Anti-Inflammatory & Anti-Allergy Agents (2003), 2(2), 191-218 incorporada por referencia en la presente.

De conformidad con varias modalidades del quinto aspecto de la presente invención, se proporcionan combinaciones de los compuestos de la presente invención con uno o más agentes seleccionados del grupo que consiste de COX-2 inhibidores, NSAIDS, aspirina, acetaminofen, triptanos, ergotamina y cafeína para el tratamiento de migraña.

De conformidad con el sexto aspecto de la presente invención, se proporcionan in vivo métodos no terminales para identificar los compuestos anti-migraña.

De conformidad con la primera modalidad del sexto aspecto de la presente invención, se proporciona un método in vivo no terminal de identificación de compuestos anti-migraña, que comprende administrar un receptor agonista CGRP a un mamífero, en una cantidad capaz de inducir un incremento en el flujo sanguíneo, seguido por la administración de un compuesto de prueba en una cantidad que pueda revertir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1 humanizado que tiene Trp 74, o un mamífero que expresa endógenamente RAMP1 que tiene Trp 74.

De conformidad con otra modalidad del sexto aspecto de la presente invención, se proporcionan un método in vivo no terminal de identificar compuestos anti-migraña que comprenden administrar a un mamífero, un compuesto de prueba previo a la administración de un agonista del receptor CGRP en donde el agonista del receptor CGRP se administra en una cantidad capaz de inducir un incremento en el flujo sanguíneo, y en donde el compuesto de prueba se administra en una cantidad que puede suprimir el incremento inducido por CGRP en el flujo sanguíneo, en donde el mamífero es un mamífero transgénico con RAMP1

humanizado que tiene Trp 74, o un mamífero que expresa endógenamente RAMP1 que tiene Trp 74.

De conformidad con otra modalidad del sexto aspecto de la presente invención se proporciona un método in vivo no terminal de identificar compuestos anti-migraña que comprenden administrar a un mamífero, un agonista del receptor CGRP, en una cantidad que puede inducir un incremento en el diámetro de la arteria periférica, seguido por la administración de un compuesto de prueba en una cantidad que puede invertir el incremento inducido por CGRP en el diámetro de la arteria periférica, en donde el mamífero es un mamífero transgénico con RAMP1 humanizado que tiene Trp 74, o un mamífero que expresa endógenamente RAMP1 que tiene Trp 74.

De conformidad con otra modalidad del sexto aspecto de la presente invención se proporciona un método in vivo no terminal de identificar compuestos anti-migraña que comprende administrar a un mamífero un compuesto de prueba previo a la administración de un agonista del receptor CGRP, en donde el agonista del receptor CGRP se administra en una cantidad que puede inducir un incremento en el diámetro de la arteria periférica, y en donde el compuesto de prueba se administra en una cantidad que puede suprimir el incremento inducido de CGRP en el diámetro de la arteria periférica, en donde el mamífero es un mamífero transgénico con RAMP1 humanizado que

tiene Trp 74, o un mamífero que expresa endógenamente RAMP1 que tiene Trp 74.

De conformidad con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos in vivo no terminales para identificar compuestos anti-migraña como se describen en la presente, en donde el flujo sanguíneo es flujo sanguíneo facial.

De conformidad con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos in vivo no terminales para identificar compuestos anti-migraña como se describen en la presente en donde el mamífero que expresa endógenamente RAMP1 que tiene Trp 74 es un primate no humano.

De conformidad con otras modalidades del sexto aspecto de la presente invención se proporcionan métodos in vivo no terminales para identificar compuestos anti-migraña como se describe en la presente en donde el mamífero que expresa endógenamente RAMP1 que tiene Trp 74 es el hombre.

De conformidad con otras modalidades del sexto aspecto de la presente invención, se proporcionan métodos in vivo no terminales para identificar compuestos anti-migraña como se describe en la presente en donde el mamífero que expresa endógenamente RAMP1 que tiene Trp 74 es un primate no humano y el primate no humano es un titi.

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De conformidad con otras modalidades del sexto aspecto de la presente invención se proporcionan métodos in vivo no terminales para identificar compuestos anti-migraña como se describe en la presente, en donde los compuestos anti-migraña son antagonistas del receptor CGRP.

Otras modalidades de la presente invención pueden comprender una combinación adecuada de dos o más de las modalidades y/o aspectos descritos en la presente.

Aún otras modalidades de la presente invención pueden comprender un subconjunto adecuado de una modalidad y/o aspecto descrito en el presente.

Todavía aún otras modalidades y aspectos de la invención serán evidentes de conformidad con la descripción que se proporciona abajo.

Breve Descripción de las Figuras

Figura 1. Análisis Schild.

La respuesta de dosis de la producción de cAMP estimulada por CGRP en ausencia (cuadrados llenos) y presencia (todos los otros) de concentraciones crecientes (de izquierda a derecha) del Ejemplo 2 antagonista CGRP. En el interior está una gráfica Schild de la relación de dosis logarítmica menos 1 (eje Y) contra concentración logarítmica del antagonista del Ejemplo 2 (eje X): pendiente = 0.94, K_b = 0.16 nM.

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Figura 2. Validación directa del flujo sanguíneo facial como substituto de la dilatación de la arteria intracraneal en la rata.

Administración intravenosa de i.v. hαCGRP induce incrementos comparables en porcentaje (100-120% de la línea base) en el diámetro de la arteria de la meninge media de la rata y flujo sanguíneo facial de la rata (barras con franjas izquierda y derecha, respectivamente). El pretratamiento con el antagonista del péptido CGRP(8-37) produce una inhibición del 50% de la administración i.v. hαCGRP intravenosa posterior para ambas medidas (barras llenas). El diámetro de la arteria intracraneal y el flujo sanguíneo facial se midieron concurrentemente en cada animal (n = 5 ratas). Los datos son la media ± sem * $p < 0.05$, ** $p<0.01$ contra el hαCGRP correspondiente solo.

Figura 3. Respuesta de dosis para hαCGRP en un flujo sanguíneo facial Doppler de láser de primate no humano.

La administración de hαCGRP induce un incremento dependiente de la dosis en un flujo sanguíneo facial Doppler con láser y primates no humanos (por ejemplo, el titi común). Los animales (n= 6) recibieron dosis crecientes de hαCGRP en intervalos de 30 minutos. Los datos son el porcentaje de cambio de picos desde la línea base ± sem, con cada animal que sirve como su control propio.

Figura 4. Inhibición de los cambios inducidos por CGRP en el flujo sanguíneo facial de primates no humanos.

El antagonista novedoso CGRP Ejemplo 2 (barras llenas) administrado previo a hαCGRP (barra en franjas), inhibe dependiente de la dosis el incremento inducido por CGRP en un flujo sanguíneo facial Doppler láser. El vehículo (barra abierta) estaba sin efecto. Los datos son la media ± sem (n = 5-6 primates por grupo). *p <0.05 comparado con CGRP solo.

Figura 5. Efecto del antagonista CGRP en la presión sanguínea del primate no humano.

En contraste con la inhibición dependiente de la dosis del flujo sanguíneo facial del primate (ver figura 4.). El ejemplo 2 tiene un efecto despreciable en la presión sanguínea (estudios en paralelo en animales por separado, n=6). Los animales recibieron dosis repetidas del Ejemplo 2 a intervalos de 20 minutos. Los datos BP son la media ± sem durante un periodo de 20 minutos medido por un brazalete en el brazo.

Descripción Detallada de la Invención

La descripción de la invención en la presente se debe construir en congruencia con las leyes y principios de enlaces químicos. Por ejemplo, puede ser necesario retirar un átomo de hidrógeno con objeto de acomodar un substituyente en cualquier ubicación dada.

Como se usa en la presente, "heterocíclico" o "heterociclo" incluye porciones cíclicas que contienen uno o más heteroátomos, (por ejemplo, O, N o S) los heterociclos incluyen aquellos que son aromáticos y aquellos que no son, esto es., "alicíclico", a menos que se especifique de otra manera.

Como se usa en la presente, el término "sistema bicíclico fusionado" cuando se describe por ejemplo, un sistema bicíclico fusionado en 5.6 contiene 1 a 4 átomos de nitrógeno incluye sistemas aromáticos y alicíclicos, por ejemplo, indolizina, indol, isoindol, 3H-indol, indolina, indazol o bencimidazol.

Si se nombra genéricamente un substituyente, entonces algunas y todas las especies de ese género comprenden ese aspecto de la invención. Por ejemplo, un substituyente genéricamente nombrado como "pirrolonilo" (el radical de "pirrolona", un pirrol que tiene un carbonilo) incluye pirrol-2-onilos en donde el carbonilo es adyacente al nitrógeno y pirrol-3-onilos en donde el carbonilo y nitrógeno tiene un metileno que interviene.

Similarmente, la presente invención comprende que se puede colocar un susbtituyente en cualquiera y todos los puntos adecuados de colocación en el substituyente a menos que se especifique de otra manera.

Sin embargo, también se entiende que los compuestos abarcados por la presente invención son aquellos que están químicamente estables esto es, substituyentes heteroalicíclicos de la presente invención no se deben colocar en una forma tal que un heteroátomo en el sustituyente heteroalicíclico sea alfa hasta un punto de colocación en donde el punto de colocación es también un heteroátomo.

Una modalidad o aspecto del cual depende otra modalidad o aspecto, describirá solamente las variables que tiene valores o disposiciones que difieren de la modalidad o aspecto de la cual dependen. Si por ejemplo, una modalidad dependiente solamente dirige R^2, entonces las variables y disposiciones no relacionadas con R^2 deben reflejar la modalidad de la cual dependen.

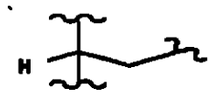
Si una variable se cuantifica con un valor de cero, entonces un enlace que se coloca a la variable ya no se debe representar.

Como se usa en la presente, "alquileno" significa un alcano divalente esto es, un alcano que tiene dos átomos de hidrógeno retirados del alcano (el hidrógeno retirado de dos átomos de carbono cuando el alcano contiene mas de un átomo de carbono, por ejemplo)

$-CH_2CH_2CH_2-$.

Como se usa en la presente, "alquilideno" significa un

alcano que tiene dos átomos de hidrógeno retirados de carbono en el alcano por ejemplo,



Se debe entender que las designaciones de enlace doble alternativo en el anillo de seis miembros en la estructura fusionada de cinco a seis miembros representada en la fórmula 1 son relativas y representan los electrones orbitales deslocalizados en π del anillo.

Como se usa en la presente , "arilo" o "ar" incluye fenilo o naftilo.

Como se usa en la presente, "heterocíclico" o "heterociclo" incluye heteroarilo y heteroalicíclico.

Como se usa en la presente, "halo" o "halógeno" incluye fluoro, cloro, bromo e Yodo y significa además uno o más halógenos iguales o diferentes que pueden estar substituidos en una porción respectiva.

A menos que se especifique de otra manera, los hidrocarburos acíclicos tales como alquilo, alcoxi, alquenilo y alquinilo pueden ser de cadena ramificada o no lineal.

Se entenderá que la presente invención puede incluir algunos y todos los estereoisómeros posibles, isómeros geométricos, diastereoisómeros, enantiómeros, anómeros e

isómeros ópticos, a menos que una descripción en particular lo especifique de otra manera.

Como se usa en la presente, "Trp74", significa que el residuo 74 es triptofano RAMP1 (Mallee et al. *J Biol Chem.* 2002, 277, 14294-8) incorporado aquí como referencia.

Como se usa en la presente "compuesto anti-migraña" incluye cualquier compuesto péptido o fragmento de péptido (modificado o sin modificar) capaz de invertir o atenuar la vasodilatación mediada por el receptor CGRP (por ejemplo, antagonistas del receptor CGRP).

Como se usa en la presente, "compuesto de prueba" incluye cualquier compuesto péptido o fragmento de péptido (modificado o no modificado) que se prueba para determinar si puede revertir o atenuar la vasodilatación mediada por el receptor CGRP (por ejemplo, antagonistas supuestos del receptor CGRP).

Como se usa en la presente, "agonista del receptor CGRP" incluye cualquier compuesto péptido o fragmento de péptido (modificado o no modificado) que puede inducir la vasodilatación mediada por el receptor CGRP particularmente por ejemplo αCGRP o βCGRP; otros miembros de la familia de la calcitonina por ejemplo, adrenomedulina; fragmentos CGRP, en la terminal N por ejemplo, CGRP(I-12) CGRP(1-15) y CGRP(1-22); amida en la terminal C (NH2) versiones de CGRP por ejemplo, CGRP(1-8+NH2), CGRP(1-13+NH2) o CGRP(1-14+NH2); y

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análogos CGRP que no se presentan naturalmente por ejemplo [Ala^{1}ψ (CH2NH)Cys^2]hCGRP que contiene un enlace pseudopéptido entre Ala^1 y Cys^2. *Ver* Maggi CA, Rovero P, Giuliani S, Evangelista S, Regoli D, Meli A. Biological activity of N-terminal fragments of calcitonin gene-related peptide. Eur J Pharmacol. 1990 Apr 10; 179(12):217-9; Qing X, Wimalawansa SJ, Keith IM. Specific N-terminal CGRP fragments mitigate chronic hypoxic pulmonary hypertension in rats. Regul Pept. 2003 Jan 31; 11 0(2):93-9; y Dennis T, Fournier A, St Pierre S, Quirion R. Structure-activity profile of calcitonin gene-related peptide in peripheral and brain tissues. Evidence for receptor multiplicity. J Pharmacol Exp Ther. 1989 Nov; 251(2):718-25 incorporado aquí como referencia.

Los compuestos de esta invención pueden existir en forma de sales farmacéuticamente aceptables. Tales sales pueden incluir sales de adición con ácidos inorgánicos tal como por ejemplo, ácido clorhídrico y ácido sulfúrico y con ácidos orgánicos tal como por ejemplo, ácido acético, ácido cítrico, ácido metansulfónico, ácido toluensulfónico, ácido tartárico, y ácido maleico. Además, en caso de que los compuestos de esta invención contengan un grupo ácido, el grupo ácido puede existir en forma de sales de metales alcalinos tales por ejemplo, una sal de potasio, y una sal de sodio; sales de metales alcalinos térreos tales como por ejemplo una sal de magnesio y una sal de calcio y sales con bases orgánicas

tales como una sal de trietilamonio y una sal de arginina. En el caso de una formulación sublingual, puede ser de beneficio en particular una sal de sacarina o sal de maleato. Los compuestos de la presente invención se pueden hidratar o no hidratar.

Los compuestos de esta invención se pueden administrar en formas tales de dosis oral como tabletas, cápsulas, (cada una de las cuales incluye formulaciones de liberación sostenida o liberación programada), píldoras, polvos, gránulos, elíxires, tinturas, suspensiones, jarabes y emulsiones. Los compuestos de esta invención también se pueden administrar intravenosamente, intraperitonealmente, subcutáneamente o intramuscularmente, todos usando formas de dosis bien conocidas por aquellos expertos en las artes farmacéuticas. Los compuestos se pueden administrar solos pero se administrarán generalmente con un portador farmacéutico seleccionado sobre la base de la ruta escogida de administración y la práctica farmacéutica estándar. También se pueden administrar los compuestos de esta invención en forma intranasal por el uso tópico de vehículos intranasales adecuados o por vías transdermales usando parches transdermales para la piel. Cuando se administra transdermalmente los compuestos de esta invención la dosis será continua a través del régimen de dosis.

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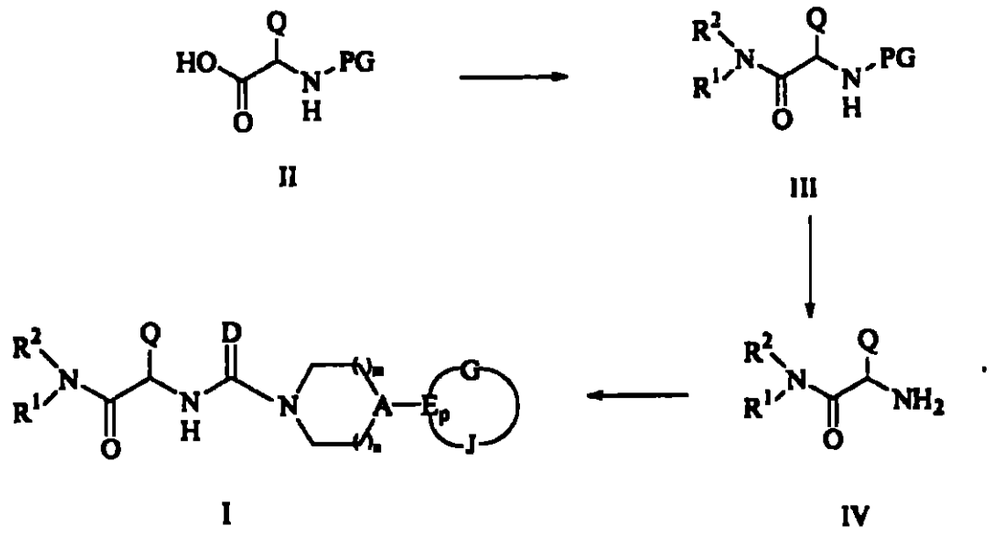
Aunque se vislumbra la dosificación desde 0.01 mg/kg a 30 mg/kg para los compuestos de la presente invención, la dosis y régimen de dosis y la programación de compuestos de la presente invención debe ajustarse cuidadosamente en cada caso, utilizando el juicio profesional sólido y considerando la edad peso y condición del receptor, la vía de administración y la naturaleza y grado de la condición de enfermedad. De acuerdo con la buena práctica clínica se prefiere administrar los compuestos actuales a nivel de concentración que produzca efectos benéficos efectivos sin provocar ningunos efectos laterales perjudiciales o indeseables.

Síntesis

Los compuestos de la presente invención se puede sintetizar de acuerdo con los esquemas de reaccion suministrados a continuación. Las variables suministradas en los esquemas a continuación se definen de acuerdo con la descripción de los compuestos en la fórmula anterior a menos que se especifique de otra manera. Los compuestos de la presente invención se pueden preparar de acuerdo con el esquema de reacción 1 o el esquema de reacción 2. También puede ser posible usar variaciones de los esquemas para preparar compuestos de las invenciones actuales, variaciones conocidas para aquellos de experiencia ordinaria en la

técnica.

Esquema de reacción 1. Síntesis de Compuestos de la Fórmula I



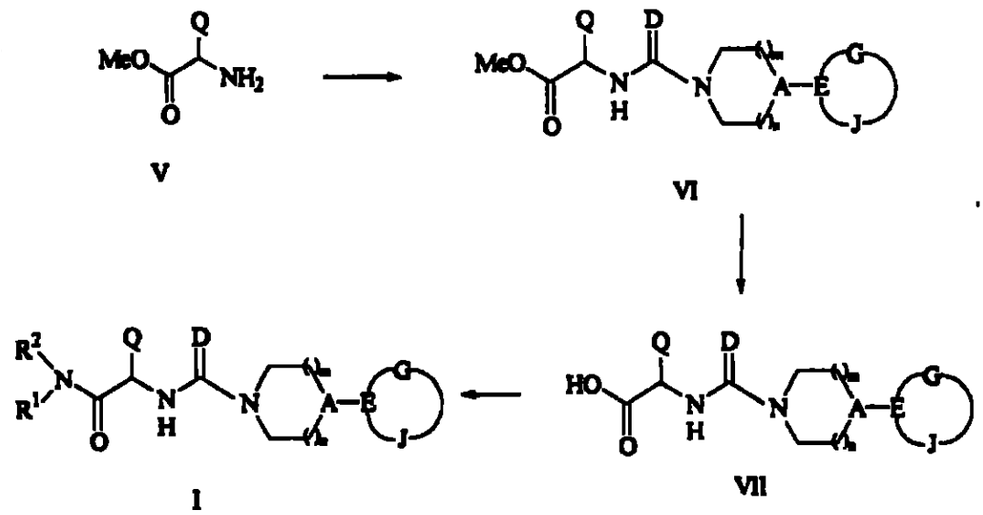
II III IV I

La síntesis descrita en el Esquema de reacción 1 inicia con un compuesto de la Fórmula **II**, que es un aminoácido con una terminación amino protegida. Los grupos protectores amino comunes (PO) incluyen BOC, CBZ, y FMOC y su adición y remoción son bien conocido en el campo. La porción de ácido carboxílico del compuesto de la Fórmula II se acopla con una amina de la Fórmula HNR^1R^2 usando reactivos de acoplamiento péptido estándar para formar una amida de la Fórmula **III**. El grupo amino protector se remueve lo que resulta en el compuesto de la Fórmula IV. Este compuesto se acopla luego con una amina de la Fórmula V (ver abajo) en una reacción de mezcla de urea o urea isóstera, lo que genera el compuesto de la Fórmula I. La formación de urea mezclada se lleva a cabo convenientemente usando fosgeno, cabonato de disuccinimidilo,

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cabonil diimidazol u otros equivalentes. La formación de urea isosteres, tal como cianoguanidinas y sulfonilguanidinas, se conocen en la literatura.

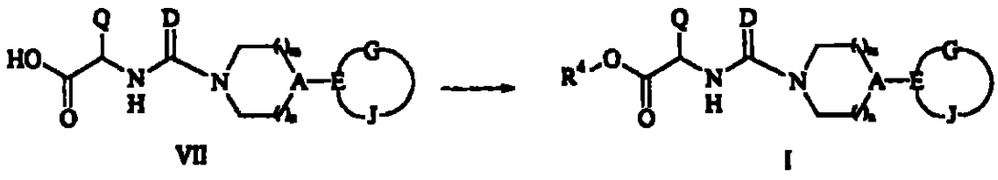
Esquema de reacción 2. Síntesis de Compuestos de la Fórmula I



La síntesis descrita por el Esquema de reacción 2 inicia con un compuesto de la Fórmula V, que es un aminoácido con una terminación de carboxilato protegida. La protección generalmente es un éster de metilo, pero otros grupos protectores tales como ésteres de etilo, t-butilo, y bencilo también pueden usarse. El compuesto de la Fórmula V se acopla con una amina de la Fórmula VIII (ver abajo) en una reacción de mezcla de urea o urea isóstera, como arriba, para generar un compuesto de la Fórmula VI. El compuesto de la Fórmula VI se convierte a un compuesto de ácido libre de la Fórmula VII que luego se acopla con una amina de la Fórmula HNR^1R^2 para generar el compuesto de la Fórmula I.

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Esquema de reacción 3. Síntesis de los compuestos de la Fórmula I

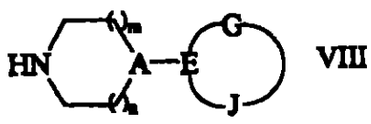


VII I

La síntesis descrita por el Esquema de reacción 3 inicia con un compuesto de la Fórmula VII del Esquema de reacción 2. El compuesto de la Fórmula V se acopla con un alcohol, R^4-OH. Tales reacciones que forman éster son bien conocidas en el arte y pueden llevarse a cabo, por ejemplo, con agentes de acoplamiento de carbodiimida tales como N,N-diciclohexilcarbodiimida. Además, es frecuentemente ventajoso, especialmente para ésteres de alcoholes secundarios y terciarios, incluir aditivos que aceleren las acilaciones tal como 4-dimetilaminopiridina.

Preparación de HNR^1R^2 y aminas de la Fórmula VIII

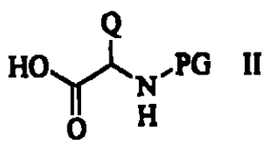
Las aminas de la Fórmula VIII y HNR^1R^2 están comercialmente disponibles, se hacen por los métodos de la literatura o se describen en la presente.

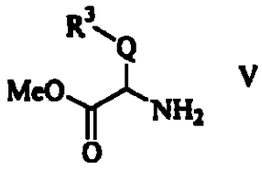


VIII

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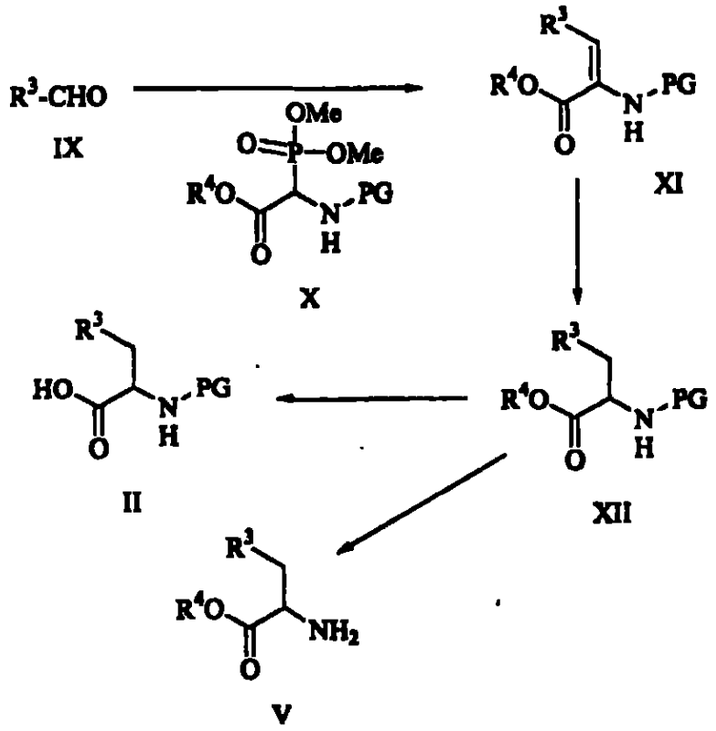
Preparación de aminoácidos de la Fórmula II y Fórmula V





Los aminoácidos de la Fórmula II y Fórmula V pueden estar comercialmente disponibles o hacerse como se describe en el Esquema de reacción 4.

Esquema de reacción 4. Síntesis de Compuestos de la Fórmula II y Fórmula V

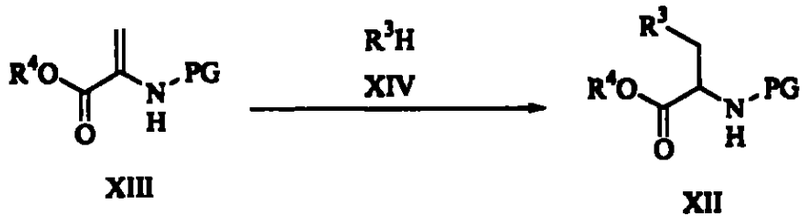


La síntesis descrita en el Esquema de reacción 4 inicia con un aldehído de la Fórmula IX, que se hace reaccionar con

un fosfonato de glicina de la Fórmula X en una reacción de acoplamiento Wadsworth-Emmons. El compuesto de la Fórmula X se desprotona con una base tal como diazabicicloundeceno o tetrametilguanidina u otras bases orgánicas e inorgánicas bien conocidas en el arte. El enlace doble del compuesto de la Fórmula XI resultante se reduce para dar compuestos de la Fórmula XII. La reducción puede llevarse a cabo para dar ya sea un racemato o por uso de un catalizador estereoselectivo para dar cualquier enantiómero de la Fórmula XII. Tales reducciones pueden resultar de la hidrogenación de transferencia a partir de donadores de hidrógeno tales como ácido fórmico o ciclohexadieno, o hidrogenación usando hidrógeno gaseoso, ambos en presencia de un catalizador apropiado. Los compuestos de la Fórmula II se preparan por hidrólisis ácida o base del éster. Los compuestos de la Fórmula V se preparan por la remoción del grupo protector (PG) usando métodos bien conocidos en el arte.

Otros derivados de aminoácido de la Fórmula XII pueden prepararse como se muestra en el Esquema de reacción 5.

Esquema de reacción 5. Síntesis de la Fórmula XII

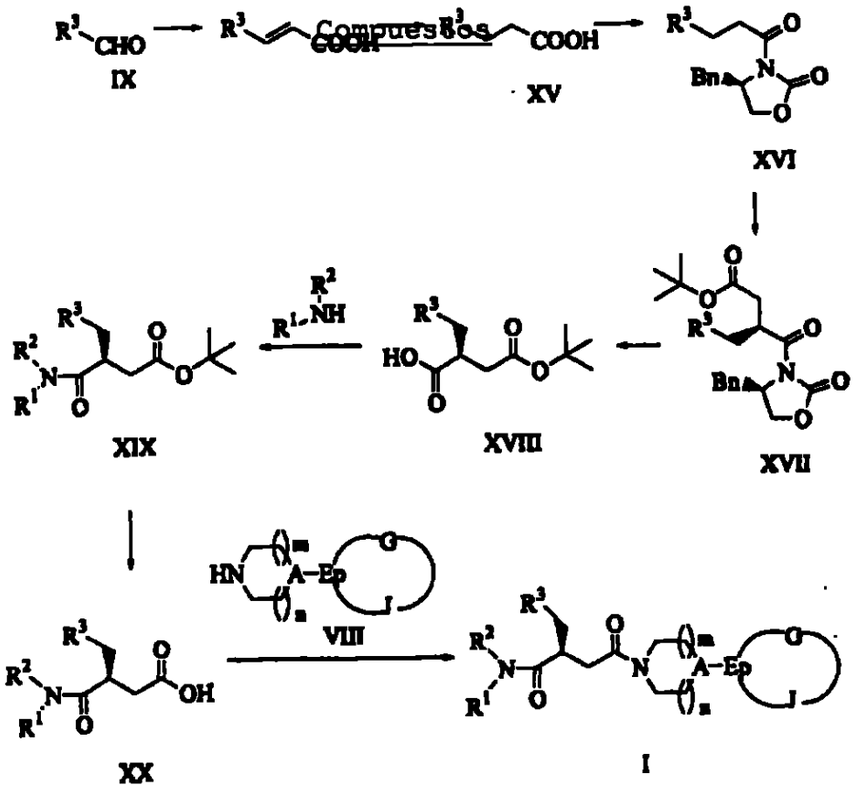


XIII XII

Donde, para los propósitos del Esquema de reacción 5, los compuestos de la Fórmula XIV son compuestos nucleofílicos tal como aminas o alcoholes que son capaces de participar en una reacción Michael con un compuesto de la Fórmula XIII como se muestra.

Otros compuestos de la Fórmula I pueden prepararse de conformidad con el Esquema de reacción 6 ó Esquema de reacción 7. También es posible usar variaciones de los esquemas para preparar los compuestos de las presentes invenciones, las variaciones conocidas por aquellos de habilidad ordinaria en el arte.

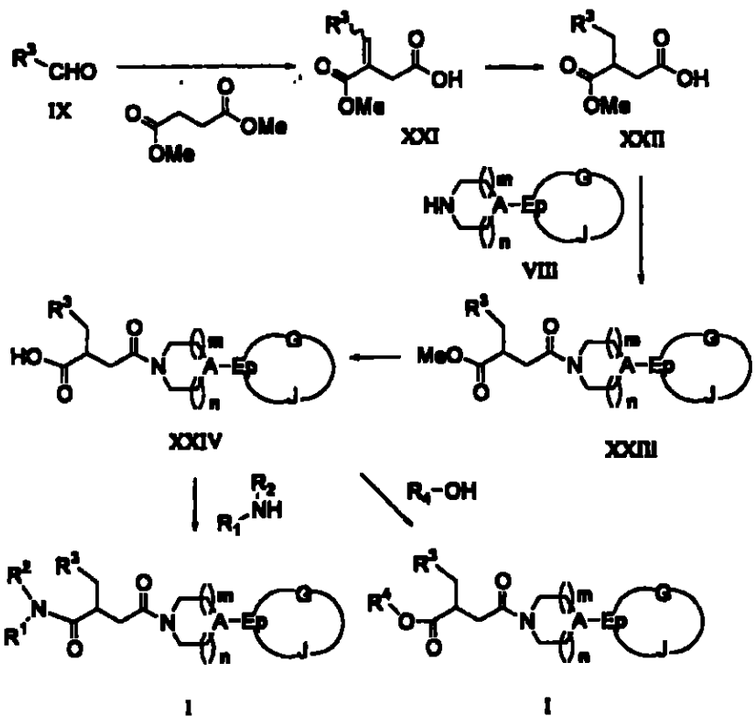
Esquema de reacción 6. Síntesis de Compuestos de la Fórmula I



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La síntesis descrita en el Esquema de reacción 6 inicia con aldehídos comercialmente disponibles o sintetizados. La homologación de dos carbonos y la reducción de enlace doble son bien conocidas en la literatura y llevan a compuestos de la Fórmula XV. Algunos compuestos de la Fórmula XV también están comercialmente disponible y otros pueden prepararse por otros métodos bien conocidos en el arte. La preparación de los compuestos de la Fórmula XVI y XVII se conoce en la literatura como substratos y productos de la síntesis asimétrica quiral Evans. La hidrólisis lleva a los compuestos de la Fórmula XVIII. Como con los compuestos de la Fórmula VII en el Esquema de reacción 2, estos ácidos carboxílicos pueden reaccionar con aminas de la Fórmula R^1R^2NH para proporcionar compuestos de la Fórmula XIX usando protocolos de acoplamiento de amida bien conocidos. La hidrólisis del éster de tert-butilo lleva a los compuestos de la Fórmula XX, que pueden además acoplarse con compuestos de la Fórmula VIII para proporcionar compuestos de la Fórmula I.

Esquema de reacción 7. Síntesis de Compuestos de la Fórmula I

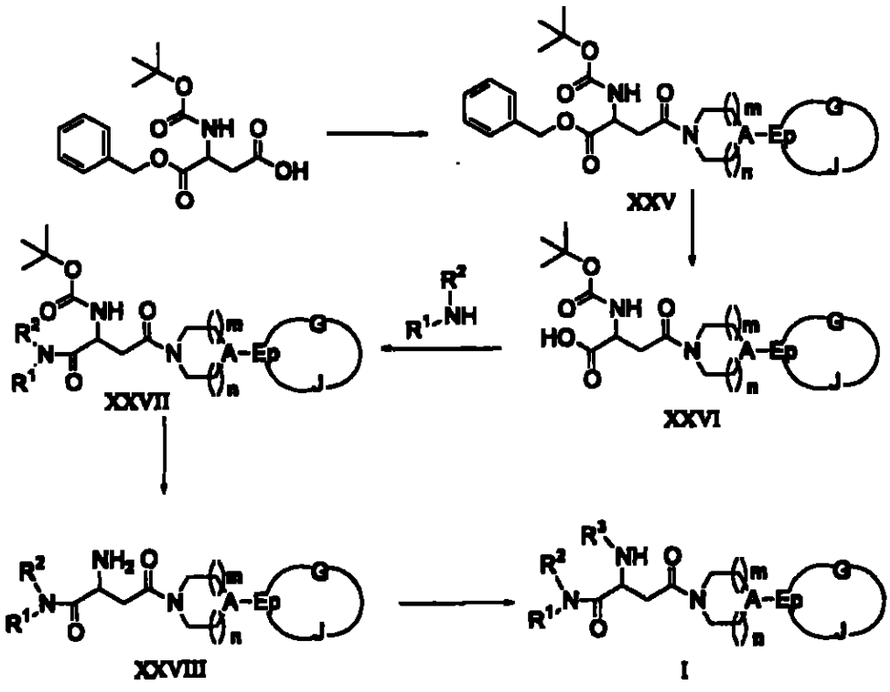


El Esquema de reacción 7 también inicia con aldehídos comercialmente disponible o sintetizados. Estos se hacen reaccionar con dimetil succinato en presencia de bases para dar compuestos de la Fórmula XXI. El enlace doble del compuesto de la Fórmula XXI se reduce para dar compuestos de la Fórmula XXII. La reducción puede llevarse a cabo para dar ya sea un racemato o por el uso de un catalizador estereoselectivo para dar cualquier enantiómero de la Fórmula XXII. Tales reducciones pueden resultar de hidrogenación de transferencia a partir de donadores de hidrógeno tal como ácido fórmico o ciclohexadieno, o hidrogenación usando hidrógeno gaseoso, ambos en presencia de un catalizador apropiado. El acoplamiento de amida con aminas de la Fórmula VIII

lleva a compuestos de la Fórmula XXIII usando protocolos de síntesis de amida bien conocidos. La hidrólisis del éster de metilo lleva a compuestos de la Fórmula XXIV, que se acoplan adicionalmente con varias aminas o alcoholes para dar amidas de la Fórmula I y ésteres de la Fórmula I, respectivamente.

Los compuestos de la Fórmula I también pueden prepararse de conformidad con el Esquema de reacción 8.

Esquema de reacción 8. Síntesis de Compuestos de la Fórmula I

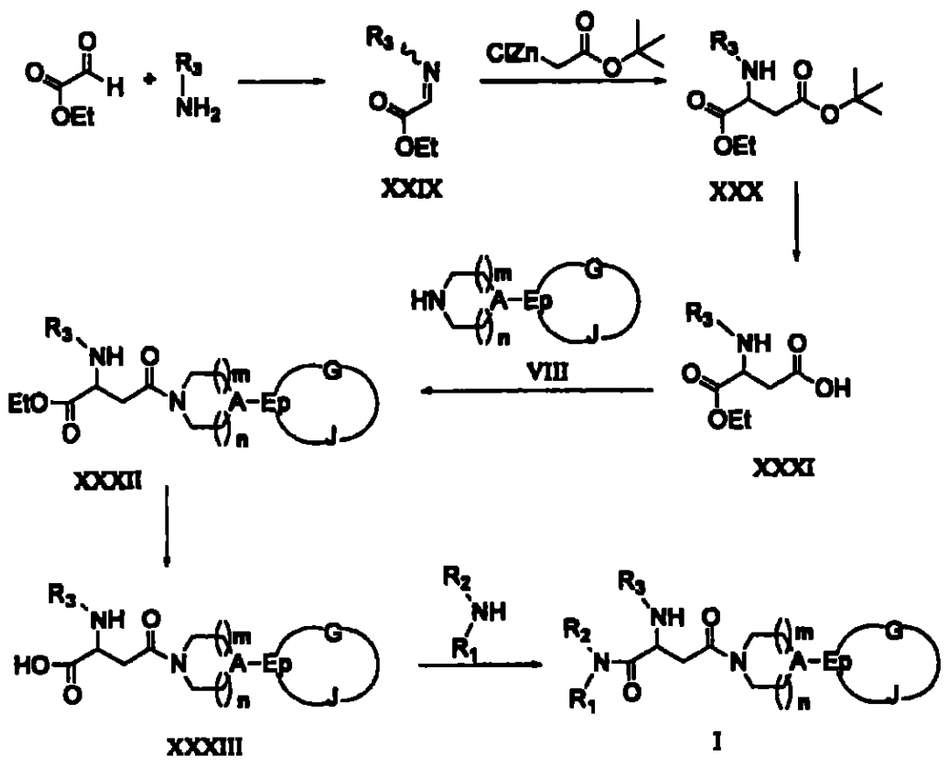


La síntesis descrita en el Esquema de reacción 8 inicia con un éster de bencilo del ácido N-tert-butiloxicarbonil-L-aspártico comercialmente disponible. Los derivados del ácido aspártico diferentemente protegidos también pueden usarse para

conveniencia sintética. El grupo beta carboxilo se acopla con aminas de la Fórmula VIII usando protocolos de acoplamiento péptido estándar. El grupo protector alfa-carboxilo del compuesto de la Fórmula XXV se remueve por hidrogenólisis dando los compuestos de la Fórmula XXVI. Estos además se acoplan con aminas de la Fórmula HNR^1R^2 para dar compuestos de la Fórmula XXVII. El grupo amino protector se remueve por tratamiento con ácidos fuertes tal como ácido trifluoroacético o cloruro de hidrógeno en solventes orgánicos. Los compuestos resultantes de la Fórmula XXVIII se hacen reaccionar luego con una variedad de reactivos electrofílicos para generar los compuestos de la Fórmula I. Por ejemplo, pueden acoplarse con compuestos halo-aromáticos usando métodos conocidos que involucran calentamiento a varias temperaturas o por catálisis con metales de transición tal como paladio o cobre, ya sea en cantidades estoiquiométricas o como catalizador. También pueden hacerse reaccionar con varios aldehídos o cetonas bajo condiciones de alquilación reductiva, bien descritos en el arte. También pueden reaccionar con isocianatos, cloruros de acilo, o cloruros de carbamoilo para generar urea, amida o derivados de carbamato, respectivamente. Se entenderá que la secuencia de las modificaciones descritas arriba pueden cambiarse dependiendo de la selección de grupos protectores y el orden de su remoción.

Los compuestos de la Fórmula I también pueden prepararse de conformidad con el Esquema de reacción 9.

Esquema de reacción 9. Síntesis de Compuestos de la Fórmula I



La síntesis descrita en el Esquema de reacción 9 inicia con una imina de la Fórmula XXIX, preparada por condensación de glioxalato de etilo y aminas de la Fórmula R^3-NH_2. Estos se hacen reaccionar con cloruro de 2-tert-butoxi-2-oxoetilzinc para dar compuestos de la Fórmula XXX. El tratamiento con ácidos fuertes remueve el grupo protector de éster de tert-butilo para dar ácidos libres de la Fórmula XXXI que se acoplan a aminas de la Fórmula VIII para proporcionar compuestos de la Fórmula XXXII. El éster de etilo se hidroliza con una sal de hidróxido de metal o base acuosa para dar los ácidos alfa libres de la Fórmula XXXIII. Estos, nuevamente se acoplan con aminas de la Fórmula HNR^1R^2 para dar compuestos de la

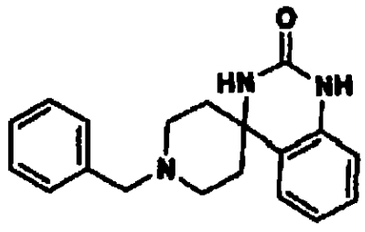
CBT 447

Fórmula I.

Intermediarios de ureidoamida y Ejemplos

General. Los espectros ^{1}H- y ^{13}C-RNM se corrieron en un instrumento Bruker de 500 ó 300 MHz y los giros químicos se reportaron en ppm (δ) con referencia a tetrametilsilano (δ = 0.0). Todas las evaporaciones se llevaron a cabo bajo presión reducida. A menos que se establezca de otra manera, el análisis CL/EM se llevó a cabo en un instrumento Shimadzu usando una columna YMC C18 (3 x 50 mm) empleando un gradiente lineal de 2 min de 0% hasta 100% del solvente B en A en una corrida de 3 min. Para CL/EM y para el sistema de CLAR preparativa Shimadzu, el Solvente A- fue: 10% metanol/90% ácido trifluoroacético, y el Solvente B fue 90% metanol/10% agua/0.1% ácido trifluoroacético con un detector UV ajustado a 220 nm.

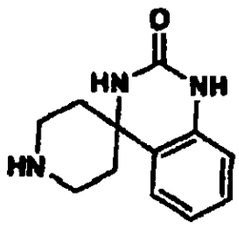
1-bencil-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'(1'H)-quinazolina



Ácido polifosfónico (113 g) se calentó a 100-110°C y se agitó mientras la 1-bencil-piperidin-4-ona (9.27 ml, 50 mmol) se agregó. Inmediatamente después, fenil urea (9.55 g, 70.

mmol) se agregó en porciones suficientemente pequeñas para evitar la espuma excesiva. La mezcla se calentó durante la noche. Luego se agregó agua (200 mL) lentamente a la mezcla la cual se permitió enfriar hasta 100-110°C (a temperaturas inferiores la mezcla se volvió demasiado viscosa para agitar). La solución resultante se neutralizó con 10 N hasta ca. pH 8, y luego se extrajo con cloroformo. La fase orgánica se secó con sulfato de magnesio y luego se concentró para dar el producto crudo el cual se purificó por cromatografía de columna instantánea en gel de sílice (acetato de etilo/hexanos 6:4) para dar el producto deseado (9.0 g, 58%). Espectro de masa: 308.25 $(MH)^+$.

2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'(1'H)-quinazolina

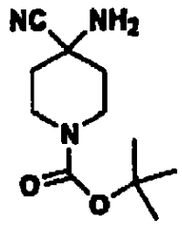


A una solución de 1-bencil-2',3'-dihidro-2'-oxoespiro-[piperdin-4,4'(1'H)-quinazolina (1.00 g) en metanol desgasificado (50 ml) y ácido clorhídrico 6N (2.0 ml) se agregó 10% carbón mineral peletizado (150 mg). La mezcla se agitó en un aparato Parr bajo una atmósfera de hidrógeno a 60 psi (4.218 kg/cm^2) durante la noche. CL/EM muestra una reacción incompleta. Más 10% carbón mineral peletizado (200

469 449

mg) se agregó, y la mezcla se agitó durante 2 días más. A tal punto, todo el material de partida se consumió. La mezcla se filtró y el filtrado se concentró para dar 531 mg del compuesto deseado (64%). Espectro de masa: 218.12 $(MH)^+$.

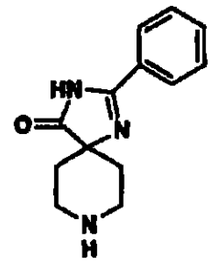
Éster de tert-butilo del ácido 4-Amino-4-ciano-piperidin-1-carboxílico



A una solución bien agitada de éster de tert-butilo del ácido 4-oxo-piperidin-1-carboxílico (9.0 g, 45.3 mmol) en metanol se agregó cloruro de amonio (2.66 g, 49.8 mmol) a temperatura ambiente y se agitó durante 1 h. El cianuro de sodio (2.44 g, 49.8 mmol) se agregó y se agitó continuamente durante 16 h adicionales. La mezcla de reacción se apagó con 5% carbonato ácido de sodio acuoso (50 mL), se diluyó con agua, y el metanol se removió por evaporación rotatoria. La cianoamina se extrajo con cloruro de metileno (3x 100 mL), se secó sobre sulfato de sodio, y los solventes se evaporaron para dar el compuesto deseado como un aceite en 91% de rendimiento. ^{1}H-RMN (300 MHz, $CDCl_3$): δ 3.95-3.90 (m, 1H), 3.80-3.71 (m, 1H), 3.42-3.06 (m, 2H), 2.04-1.94 (m, 1H), 1.71-1.50 (m, 3H). Espectro de masa: 226 $(MH)^+$.

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Clorohidrato de 2-fenil-1,3,8-triaza-espiro[4,5]dec-1-en-4-ona



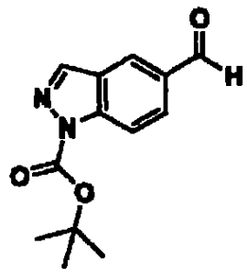
A una solución de éster de tert-butilo del ácido 4-amino-4-ciano-piperidin-1-carboxílico (1.0 g, 4.44 mmol) en cloruro de metileno (30 mL) se agregó trietilamina (1.24 mL, 8.88 mol), seguido por cloruro de benzoilo (936 mg, 6.66 mmol). Después de 30 min, 4-(dimetilamino)piridina (40 mg, 0.33 mmol) se agregó y se agitó continuamente durante 12 h adicionales. La mezcla de reacción luego se apagó con hidróxido de sodio 1M (10 mL), se diluyó con acetato de etilo (100 mL), y se separó. La capa orgánica se lavó secuencialmente con hidróxido de sodio 1M (40 mL), carbonato ácido de sodio acuoso (50 mL), y salmuera (50 mL) luego se secó sobre sulfato de sodio. El producto deseado, éster de tert-butilo del ácido 4-benzoilamino-4-ciano-piperidin-1-carboxílico se obtuvo en 90% de rendimiento a través de cristalización usando 30% acetato de etilo en hexano como un solvente.

A una solución de éster de tert-butilo del ácido 4-benzoilamino-4-ciano-piperidin-1-carboxílico (1.3 g, 4 mmol)

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en etanol (10 mL) se agregó 6M hidróxido de sodio (1.5 mL) seguido por 30% peróxido de hidrógeno. La mezcla de reacción luego se puso a reflujo durante 3 h. La mezcla de reacción luego se diluyó con agua (30 mL), y el etanol se removió. El residuo se diluyó con acetato de etilo (100 mL). La fase orgánica se lavó con salmuera (30 mL) y se secó sobre sulfato de sodio. El producto deseado, éster de tert-butilo del ácido 4-oxo-2-fenil-1,3,8-triaza-espiro[4.5]dec-1-eno-8-carboxílico se obtuvo en 80% de rendimiento a través de cristalización de 30% acetato de etilo en hexano. El éster de tert-butilo luego se disolvió en cloruro de metileno (5 mL) y una solución saturada de cloruro de hidrógeno en dioxano (25 mL) se agregó. Después de 2 h, el solvente se removió para dar clorohidrato de 2-fenil-1,3,8-triaza-espiro[4.5]dec-1-en-4-ona, como polvo blanco en 95% de rendimiento. ^{1}H-RMN (500 MHz, CD_3OD): δ 8.23-8.21 (m, 2H), 7.96-7.92 (m, 1H), 7.79-7.76 (m, 2H), 3.68-3.64 (m, 3H), 3.31-3.30 (m, 1H), 2.47-2.44 (m, 4H). Espectro de masa: 230 $(MH)^+$.

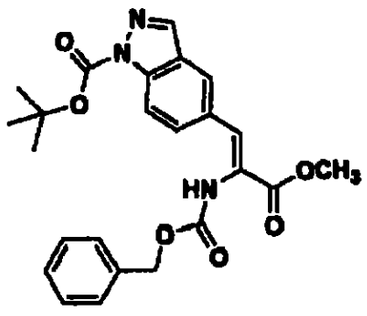
Éster de tert-butilo del ácido 5-formil-indazol-1-carboxílico



452

Una solución de cloruro de metileno (2 mL) de di-tert-butildicarbonato (388 mg, 1.78 mmol) se agregó gota a gota a temperatura ambiente a una solución de 1H-indazol-5-carbaldehído (273 mg, 1.87 mmol), 4-dimetilaminopiridina (114 mg, 0.94 mmol), y trietilamina (0.26 mL, 1.87 mmol) en cloruro de metileno (10 mL). La solución amarilla brillante resultante se agitó a temperatura ambiente durante 16 h. Los solventes se removieron in vacuo y el residuo se sometió a cromatografía instantánea con gel de sílice (25 g) y acetato de etilo/hexanos (1:1) que contienen trietilamina al 1% como eluyente para proporcionar el compuesto del título como un líquido amarillo café (414 mg, 90%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 10.08 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H) 8.25 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 1.71 (s, 9H). ^{13}CRMN ($CDCl_3$, 125 MHz) δ 191.8, 149.0, 142.5, 140.6, 133.0, 128.3, 126.4, 125.8, 115.3, 85.7, 27.8.

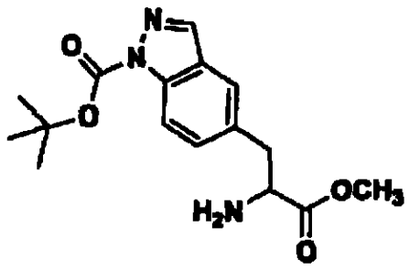
Éster de tert-butilo del ácido 5-(2-benciloxicarbonilamino-2-metoxicarbonil-vinil)-indazol-1-carboxílico



CA 453

Una solución de éster trimetil de N-(benciloxiicarbonil)-α-fosfonoglicina (5.50 g, 16.6 mmol) y tetrametilguanidina (1.99 mL, 15.9 mmol) en tetrahidrofurano anhidro (50 mL) se agitó a -78°C durante 20 min. A esto se agregó una solución de éster de tert-butilo del ácido 5-formil-indazol-1-carboxílico (3.72 g, 15.1 mmol) en tetrahidrofurano (25 mL) lentamente por medio de una jeringa durante 10 min. La mezcla de reacción se agitó a -78°C durante 4 h y luego se permitió calentar a temperatura ambiente durante la noche. El solvente se evaporó y el residuo resultante se sometió a cromatografía en columna instantánea en gel de sílice (1:2 acetato de etilo/hexano) dando el compuesto del título como una espuma blanca (5.77 g, 85%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 8.09 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 7.84 (s, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.47 (s, 1H), 7.30 (br s, 5H), 6.43 (br s, 1H), 5.09 (s, 2H), 3.84 (s, 3H), 1.72 (s, 9H). Espectro de masa: 452 $(MH)^+$.

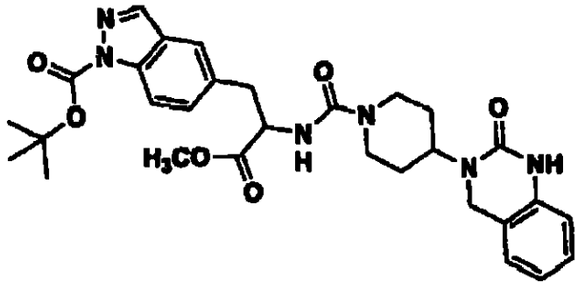
Éster de tert-butilo del ácido (±)-5-(2-Amino-2-metoxicarbonil-etil)-indazol-1-carboxílico



454

Una mezcla de éster de tert-butilo del ácido 5-(2-benciloxicarbonilamino-2-metoxicarbonil-vinil)-indazol-1-carboxílico (524 mg, 1.16 mmol) y paladio en carbono al 10% (60 mg) en metanol (20 mL) se agitó durante 4.5 h bajo 50 psi (3.515 kg/cm^2) gas de hidrógeno usando un hidrogenado Parr. La mezcla de reacción se evacuó y se purgó con nitrógeno. Luego, la mezcla de reacción se filtró a través de una almohadilla de celite y la almohadilla se enjuagó con varias porciones de metanol. El metanol filtrado se evaporó para dar el compuesto del título (351 mg, 95%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 8.12-8.10 (m, 2H), 7.55 (br s, 1H), 7.37 (dd, J = 8.9, 1.5 Hz, 1H), 3.77-3.75 (m, 1H), 3.70 (s, 3H), 3.19 (dd, J = 13.7, 5.5 Hz, 1H), 2.99 (dd, J = 13.7, 8.0 Hz, 1H), 1.72 (s, 9H). Espectro de masa: 320 $(MH)^+$.

Éster de tert-butilo del ácido (±)-5-(2-Metoxicarbonil-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-etil)-indazol-1-carboxílico

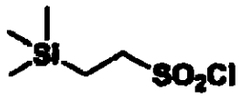


Una solución de éster de tert-butilo del ácido 5-(2-amino-2-metoxicarbonil-etil)-indazol-1-carboxílico (307 mg,

455

0.96 mmol), carbonato de N,N-disuccinimidilo (246 mg, 0.961 mmol), y N,N-diisopropiletilamina (0.67 mL, 3.84 mmol) en cloruro de metileno se agitó durante 30 min a temperatura ambiente. 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (238 mg, 1.03 mmol) se agregó y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. El solvente se evaporó y el residuo se sometió a cromatografía instantánea usando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente, da el producto (259 mg, 47%). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.13-8.10 (m, 2H), 7.48 (br s, 1H), 7.31 (dd, J = 8.8, 1.6 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.94 (t, J = 7.7 Hz, 1H), 6.82 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H), 4.98 (d, J = 7.7 Hz, 1H), 4.87-4.81 (m, 4.58-4.49 (m, 1H), 4.26 (s, 2H), 4.05-3.97 (m, 2H), 3.74-3.67 (m, 4H), 3.29-3.23 (m, 2H), 2.93-2.84 (m, 2H), 1.76-1.62 (m, 1H), 1.70 (s, 9H), 1.48-1.42 (m, 1H) Espectro de masa: 577 $(MH)^+$.

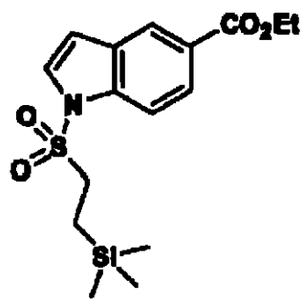
Cloruro de 2-trimetilsilanil-etansulfonilo



El cloruro de sulfurilo (43 ml, 539 mmol) se agregó en 3 min a una solución clara de trifenilfosfina (129 g, 490 mmol) en cloruro de metileno (200 mL) a 0°C en un matraz de fondo redondo de 3 cuellos secado a la flama. Después de agitar a 0°C durante 5 min, el baño de agua-hielo se removió y 2-

trimetilsililetansulfonato de etilo (50 g, 245 mmol) se agregó en porciones durante 10 min. La suspensión blanca resultante se agitó a temperatura ambiente durante 16 h, luego esto se filtró a través de una almohadilla de celite. El filtrado se concentró a ca 50 mL, acetato de etilo/hexanos (1:3, 1000 mL) y celite (40 g) se agregaron. La mezcla se agitó a temperatura ambiente durante 15 min y se filtró a través de una almohadilla de celite. Los solventes se removieron in vacuo y el residuo se cargó en una columna pre-mojada con gel de sílice (300 mL) usando 1:3 acetato de etilo/hexanos como el eluyente. Los solventes se removieron y el compuesto del título se obtuvo como un líquido marrón ligero (41.9g, 85%). Si no se usa inmediatamente, el producto final deberá almacenarse bajo nitrógeno en el congelador o refrigerador para minimizar la descomposición. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 3.61-3.57 (m, 2H), 1.32-1.27 (m, 2H), 0.10 (s, 9H).

Éster de etilo del ácido 1-(2-Trimetilsilanil-etansulfonil)-1H-indol-5-carboxílico

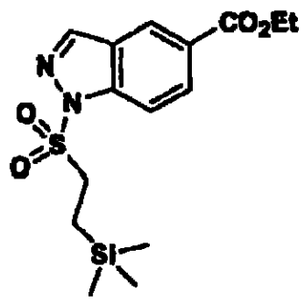


447 457

Una solución de éster de etilo del ácido 1H-indol-5-carboxílico (10.31 g, 58.8 mmol) en dimetilformamida (50 mL) se agregó gota a gota a 0°C a una mezcla de hidruro de sodio (1.83 g, 76.4 mmol) en dimetilformamida (150 mL). La mezcla resultante se agitó a 0°C durante 30 min, luego una solución de cloruro de 2-trimetilsilanil-etansulfonilo (17.7 g, 88.2 mmol) en dimetilformamida (100 mL) se agregó lentamente a 0°C a la mezcla anterior. Después de 2 h, cloruro de amonio acuoso saturado (200 mL) se agregó, y la mezcla se extrajo con acetato de etilo (300 mL). Después de la separación, la capa acuosa se extrajo con acetato de etilo (2 x 150 mL). Las capas orgánicas combinadas se lavaron con salmuera (3 x 150 mL), y se secaron sobre sulfato de sodio anhidro. Los solventes se removieron in vacuo y el residuo se sometió a cromatografía instantánea en gel de sílice usando 1:1.5 cloruro de metileno/hexanos como eluyente para proporcionar el compuesto del título como un sólido blanco (15.8 g, 79%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 8.36 (d, J = 1.5 Hz, 1H), 8.03 (dd, J = 9.0, 2.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 3.5 Hz, 1H), 6.75 (d, J = 3.5 Hz, 1H), 3.94 (s, 3H), 3.21-3.18 (m, 2H), 0.84-0.80 (m, 2H), -0.06 (s, 9H). ^{13}C-RMN ($CDCl_3$, 125 MHz) δ 167.3, 137.7, 130.3, 128.3, 125.9, 125.5, 124.0, 112.8, 108.3, 52.2, 51.2,10.1, -2.1. Espectro de masa 354.12 $(MH)^+$.

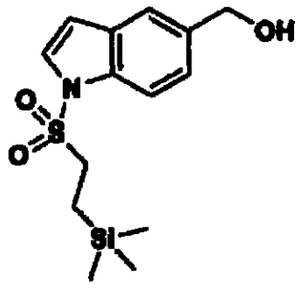
Preparado similarmente:

Éster etilo del ácido 1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-carboxílico



^{1}H-RMN ($CDCl_3$, 500 MHz) δ 8.51 (s, 1H), 8.34 (s, 1H), 8.21 (dd, J = 8.9, 1.5 Hz, 1H), 8.12 (d, J = 9.2 Hz, 1H), 3.96 (s, 3H), 3.42-3.39 (m, 2H), 0.86-0.82 (m, 2H), -0.02 (s, 9H). ^{13}C-RMN ($CDCl_3$, 125 MHz) δ 166.4, 143.1, 141.2, 130.1, 126.5, 125.0, 124.2, 112.9, 52.5, 51.3, 9.8, -2.1. Espectro de masa 355.13 $(MH)^+$.

[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-metanol

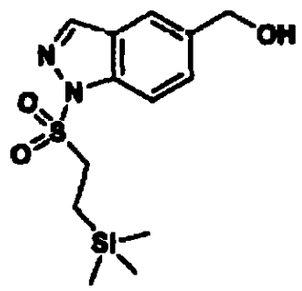


Una solución de hidruro de diisobutilaluminio (82.9 mL, 1M en tolueno, 82.9 mmol) se agregó lentamente a 0°C a la solución de éster de etilo del ácido 1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-carboxílico (8.81 g, 25.9 mmol) en

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tolueno (200 mL). Después esto se agitó a 0°C durante 45 min, la reacción se apagó por la adición de metanol (26 mL), pulverizado con decahidrato de sulfato de sodio (194 g) y celite (26 mL). La mezcla se calentó hasta temperatura ambiente en 1 h y se filtró a través de una almohadilla de celite. Los solventes se removieron para proporcionar el compuesto del título como un líquido muy viscoso, el cual se solidificó durante enfriamiento. Un sólido blanco (8.08 g, 100% de rendimiento). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.44 (d, J = 3.7 Hz, 1H), 7.35 (dd, J = 8.6, 1.5 Hz, 1H), 6.66 (d, J = 3.7 Hz, 1H), 4.79 (s, 2H), 3.18-3.14 (m, 2H), 1.73 (s, 1H), 0.85-0.82 (m, 2H), -0.06 (s, 9H). Espectro de masa 312.14 $(MH)^+$.

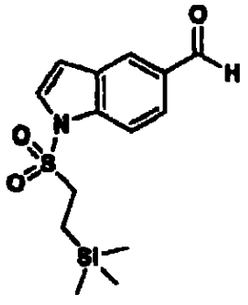
[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-metanol



Una solución de éster de etilo del ácido 1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-carboxílico (secado azeotrópicamente con tolueno (2x), 5.77g, 16.9 mmol) en tetrahidrofurano (50 mL) se agregó a 0°C a una mezcla de borohidruro de litio (3.68 g, 169 mmol) en tetrahidrofurano

(100 mL). La mezcla se calentó hasta a temperatura ambiente y se agitó durante 14h. Esto se enfrió a 0°C y borohidruro de litio (3.5 g) se agregó. La mezcla se calentó hasta a temperatura ambiente y se agitó durante 14 h. Esto se volvió a enfriar a 0°C y cloruro de amonio acuoso saturado (25 mL) se agregó lentamente. La suspensión blanca resultante se filtró a través de una almohadilla de celite, los solventes se removieron y el residuo se sometió a cromatografía instantánea usando acetato de etilo/hexanos (1:1.5) con 1% trietilamina para proporcionar el compuesto del título como un sólido blanco (3.8 g, 72%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.41 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.85 (s, 1H), 7.61 (dd, J = 8.5, 1.2 Hz, 1H), 4.76 (s, 2H), 3.49-3.46 (m, 2H), 0.76-0.72 (m, 2H), -0.03 (s, 9H); ^{13}C-RMN (CD_3OD, 125 MHz) δ 141.2, 140.9, 138.3, 129.2, 125.8, 119.6, 112.7, 63.8, 50.8, 9.9, -3.2. Espectro de masa 313.12 $(MH)^+$.

1-(2-Trimetilsilanil-etansulfonil)-1H-indol-5-carbaldehído



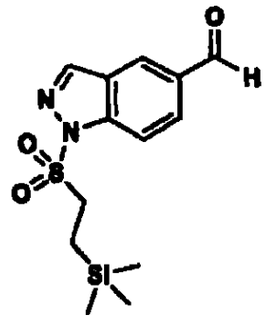
Una solución de [1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-metanol (2.1 g, 6.74 mmol) en cloruro de metileno

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(30 mL) se agregó a 0°C a una mezcla de dióxido de manganeso activado (22 g, secado azeotrópicamente con tolueno (2x)) y cloruro de metileno (70 mL) en un matraz de fondo redondo a 500 mL. La mezcla de reacción se agitó a 0°C durante 30 min y se filtró a través de una almohadilla de celite. Los solventes se removieron in vacuo para proporcionar el compuesto del título como un sólido blanco (1.8 g, 80%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 10.06 (s, 1H), 8.15 (s, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.87 (dd, J = 8.6, 1.5 Hz, 1H), 7.54 (d, J = 3.4 Hz, 1H), 6.80 (d, J = 3.6 Hz, 1H), 3.24-3.20 (m, 2H), 0.86-0.82 (m, 2H), -0.06 (s, 9H). ^{13}C-RMN ($CDCl_3$, 125 MHz) δ 191.9, 138.5, 132.3, 130.7, 128.8, 125.3, 125.1, 1134.6, 108.4, 51.4, 10.2, -2.1. Espectro de masa 310.12 $(MH)^+$.

Preparado similarmente:

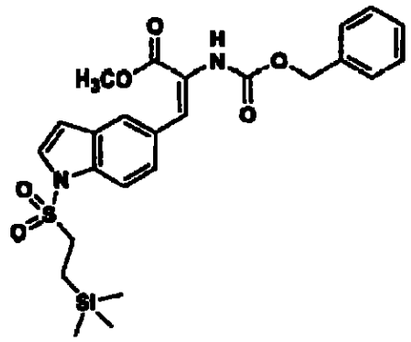
1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-carbaldehído



Espectro de masa 311.10 $(MH)^+$.

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Éster de metilo del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-acrílico



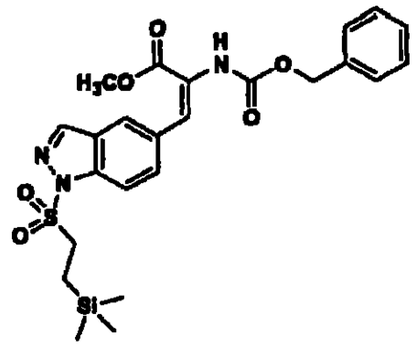
1,1,3,3-Tetrametilguanidina (0.68 mL, 5.43 mmol) se agregó a temperatura ambiente a una solución de éster de trimetilo de N-(benciloxicarbonil)-α-fofonoglicina (1.88 g, 5.69 mmol) en tetrahidrofurano (40 mL). La mezcla se agitó a temperatura ambiente durante 15 min y se enfrió a -78°C y una solución de 1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-carbaldehído (1.6 g, 5.17 mmol) en tetrahidrofurano (15 mL) se agregó lentamente. La mezcla de reacción resultante se agitó a -78°C durante 2h y luego se calentó a temperatura ambiente en 3h. Los solventes se removieron in vacuo y el residuo se sometió a cromatografía instantánea en gel de sílice usando cloruro de metileno/hexanos (1:1.5) con trietilamina al 1% como eluyente para proporcionar el compuesto del título como una mezcla 92:8 Z/E (determinado por la integración de CO_2CH_3, para el isómero Z a 3.79 ppm, e isómero E a 3.65 ppm). Para el isómero Z: ^{1}H-RMN (CD_3CN, 500 MHz) δ 7.96 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.66 (d, J =

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8.5 Hz, 1H), 7.56 (d, J = 3.7 Hz, 1H), 7.51 (s, 1H), 7.43-7.35 (m, 5H), 7.67 (d, J = 3.7 Hz, 1H), 5.16 (s, 2H), 3.79 (s, 3H), 3.42-3.38 (m, 2H), 0.87-0.83 (m, 2H), -0.04 (s, 9H). Espectro de masa 515.20 $(MH)^+$.

Preparado similarmente:

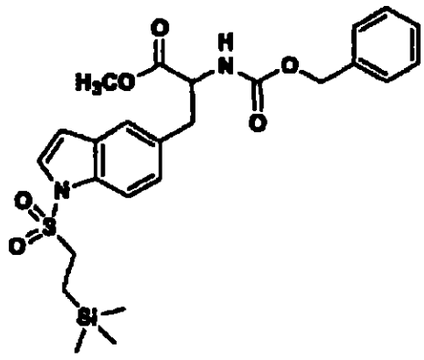
Éster de metilo del ácido 2-benciloxicarbonilamino-3-[1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-il]-acrílico



La cromatografía instantánea en gel de sílice usando cloruro de metileno que contienen 1% trietilamina como eluyente proporciona el compuesto del título como una mezcla 95:5 Z/E (determinado por la integración de -CH=C(CO_2Me)(NHCBz), 3.72 g, 92%). Para el isómero Z: ^{1}H-RMN (CD_3CN, 500 MHz) δ 8.39 (s, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.8 Hz, 1 H), 7.84 (dd, J = 8.8, 1.2 Hz, 1H), 7.51 (s, 1H), 7.43-7.35 (m, 5H), 5.14 (s, 2H), 3.81 (s, 3H), 3.51-3.47 (m, 2H), 0.83-0.79 (m, 2H), -0.02 (s, 9H). Espectro de masa 516.18 $(MH)^+$.

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Éster de metilo del ácido (±)-2-amino-3-[1,(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-propiónico

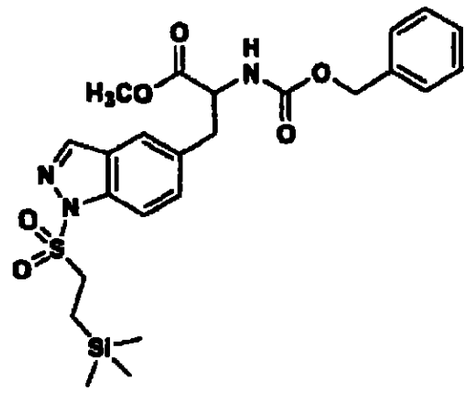


A una matraz de fondo redondo de 500 mL secado a la flama se agregó éster de metilo del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-acrílico (2.24 h, 4.36 mmol), metanol (100 mL) y paladio en carbón mineral al 10% (0.52 g). La mezcla se desgasificó y se purgó con hidrógeno 5 veces. Esto se agitó a temperatura ambiente durante 1 h y se filtró a través de una almohadilla de celite. Los solventes se removieron y el residuo se sometió a cromatografía instantánea usando acetato de etilo/hexanos (1:1 y 2:1) que contienen trietilamina al 1% para proporcionar el compuesto del título como un líquido viscoso incoloro (1.27g, 76%), el cual se solidificó durante enfriamiento. ^{1}H-RMN (CD_3CN, 500 MHz) δ 7.82 (d, J = 8.2 Hz, 1H), 7.51-7.49 (m, 2H), 7.22 (dd, J = 8.6, 1.5 Hz, 1H), 6.72 (d, J = 3.7 Hz, 1H), 3.70 (dd, J = 7.3, 6.1 Hz, 1H), 3.65 (s, 3H), 3.38-3.34 (m, 2H), 3.08 (dd, J =

13.4, 5.8 Hz, 1H), 2.95 (dd, J = 13.4, 7.3 Hz, 1H), 0.82-0.79 (m, 2H), -0.05 (s, 9H). ^{13}C-RMN ($CDCl_3$, 125 MHz) δ 176.0, 134.4, 133.4, 131.1, 127.9, 126.4, 122.4, 113.1, 107.7, 56.6, 51.7, 50.8, 41.3, 10.1, -2.7. Espectro de masa 383.16 (MH)+.

Preparado similarmente:

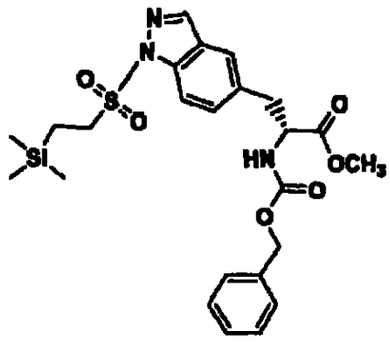
Éster de metilo del ácido (±)-2-amino-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]propiónico



^{1}H-RMN (CD_3CN, 500 MHz) δ 8.34 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.46 (dd, J = 8.6, 1.5 Hz, 1H), 3.71 (dd, J = 7.3, 5.8 Hz, 1H), 3.65 (s, 3H), 3.48-3.44 (m, 2H), 3.12 (dd, J = 13.7, 5.8 Hz, 1H), 2.97 (dd, J = 13.7, 7.6 Hz, 1H), 0.83-0.79 (m, 2H), -0.02 (s, 9H). ^{13}C-RMN ($CDCl_3$, 125 MHz) δ 175.9, 141.1, 140.5, 134.6, 131.5, 126.0, 122.2, 112.7, 56.4, 51.8, 51.1, 40.9, 9.8, -2.6. Espectro de masa 384.15 $(MH)^+$.

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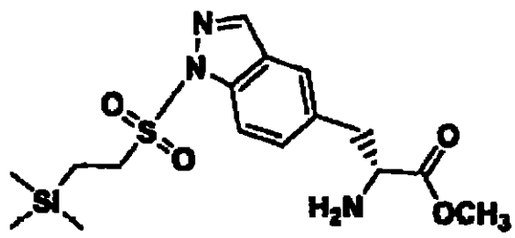
Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



En una bolsa de guante que se sometió a 3 ciclos de purga de vacío/nitrógeno, un matraz de reacción AIRFREE® (Schlenk) equipado con una barra de agitación se cargó con trifluorometilsulfonato (-)-1,2-bis((2R,5R)-2,5-dietilfosfolano)benceno(ciclooctadieno)rodio (I) (123 mg, 0.17 mmol, 5 mol%), sellado con un septo de hule, y se removió de la bolsa de guante. El éster de metilo del ácido 2-benciloxicarbonilamino-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-acrílico (1.75 g, 3.40 mmol) se pesó en un segundo matraz de reacción AIRFREE® (Schlenk) equipado con una barra de agitación y sellado con un septo de hule. Después de 3 ciclos de purga de vacío/nitrógeno, esto se disolvió en una mezcla de metanol anhidro (75 mL) y cloruro de metileno anhidro (15 mL). Ambos solventes se desoxigenan antes de la adición al burbujeo con nitrógeno durante al menos 1 h. Una vez en solución, la mezcla se volvió a someter a 3 ciclos de purga de vacío/nitrógeno. La solución de deshidroamino ácido se introdujo en el matraz de reacción

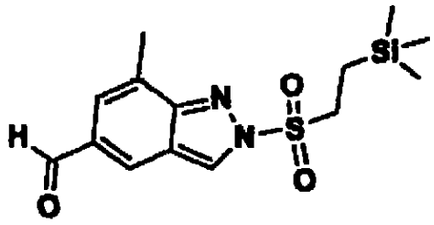
AIRFREE® (Schlenk) que contienen el catalizador por medio de cánula. La mezcla de reacción se sometió a 5 ciclos de purga de vacío/hidrógeno antes de abrir el matraz a 1 atm. De hidrógeno (globo). Después de 16 h, la mezcla de reacción se purgó con 3 ciclos de purga de vacío/nitrógeno. El solvente se evaporó y el residuo se sometió a cromatografía en columna (gradiente 1:4 acetato de etilo/hexanos hasta 1:2 acetato de etilo/hexanos) para dar 1.5 g (85%) del compuesto del título como un sólido blanco con 98.4% ee como se determina por el análisis CLAR usando una columna Chirocel OD con 80% hexano/20% etanol como eluyente (tiempo de retención: 13.9 min para el compuesto del título y 11.2 min para enantiómero S). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.17 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.35-7.25 (m, 6H), 5.29-5.24 (m, 1H), 5.08 (dd, J = 19.0, 12.1 Hz, 2H), 4.73-4.67 (m, 1H), 3.73 (s, 3H), 3.38-3.32 (m, 2H), 3.29 (dd, J = 14.2, 5.6 Hz, 1H), 3.19 (dd, J = 13.9, 5.6 Hz, 1H), 0.91-0.85 (m, 2H), -0.02 (s, 9H). Espectro de masa: 518 $(MH)^+$.

Éster de metilo del ácido (R)-2-Amino-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



Una mezcla de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico (1.24 g, 2.40 mmol) y paladio en carbono al 10% (124 mg) en metanol (50 mL) se agitaron durante 2 h bajo 50 psi (3.51 kg/cm^2) hidrógeno usando un hidrogenador Parr. La mezcla de reacción se purgó con 3 ciclos de purga de vacío/nitrógeno. La mezcla de reacción luego se filtró a través de una almohadilla de celite y la almohadilla se enjuagó con varias porciones de metanol. El metanol filtrado se evaporó para dar 879 mg (96%) del compuesto del título como una goma pegajosa. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.59 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 3.72 (s, 3H), 3.38-3.32 (m, 2H), 3.21 (dd, J = 13.9, 5.1 Hz, 1H), 2.98 (dd, J = 13.9, 7.9 Hz, 1H), 0.91-0.85 (m, 2H), -0.02 (s, 9H). Espectro de masa: 384 $(MH)^+$.

7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-carbaldehído

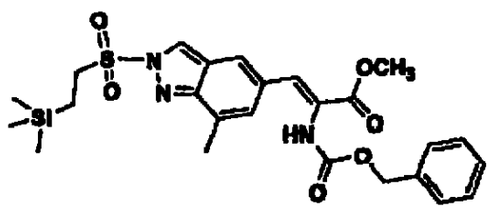


A una suspensión de 5-aldehído de 7-metilindazol (3.0 g, 18.7 mmol) en cloruro de metileno (150 mL) se agregó

U8T469

trietilamina (7.83 mL, 56.2 mL, 3 equiv) seguido por gota a gota adición de cloruro de 2-Trimetilsilanil-etansulfonilo puro (5.60 g, 28.1 mmol, 1.5 equiv). La mezcla se volvió gradualmente homogénea y se dejo agitar a temperatura ambiente durante 16 h. La solución se concentró a una cantidad mínima de cloruro de metileno y luego se sometió a cromatografía en columna instantánea en gel de sílice (1:4 acetato de etilo/hexanos) para dar 4.7 g (77%) del producto como un amarillo pálido. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 9.98 (s, 1H), 8.77 (s, 1H), 8.09 (s, 1H), 7.64 (s, 1H), 3.64-3.58 (m, 2H), 2.65 (s, 3H), 0.88-0.82 (m, 2H), 0.01 (s, 9H).

Éster de metilo del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(2-Trimetilsilanil-etansulfonil)-2H-indazol-5-il]-acrílico

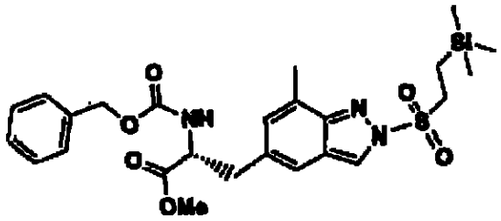


A una solución de éster de trimetilo de N-(benciloxicarbonil)-α-fosfonoglicina (4.93 g, 14.9 mmol, 1.1 equiv) en tetrahidrofurano anhidro (75 mL) se agregó tetrametilguanidina (1.78 mL, 1.05 equiv). La mezcla se agitó a temperatura ambiente bajo nitrógeno durante 5 min y luego se enfría a -78°C. Después de agitar durante 15 min a -78°C

4000 470

una solución de 7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-carbaldehído en tetrahidrofurano (25 mL) se agregó. La mezcla de reacción se permitió calentar lentamente a temperatura ambiente durante la noche. Aunque la reacción se incompletó, el solvente se evaporó. El residuo resultante se disolvió en acetato de etilo y se lavó con ácido sulfúrico 1M. La capa orgánica se separó, se secó sobre sulfato de magnesio, se filtró y se evaporó. La cromatografía en columna instantánea (1:4 acetato de etilo/hexanos) da 2.66 g (37 %) del producto como una espuma de vidrio blanca. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.48 (s, 1H), 7.62 (s, 1H), 7.38-7.25 (m, 7H), 6.48 (bs, 1H), 5.10 (s, 2H), 3.83 (s, 3H), 3.58-3.52 m, 2H), 2.51 (s, 3H), 0.89-0.83 (m, 2H), 0.02 (s, 9H). Espectro de masa: 530 $(MH)^+$.

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[7-metil-2-(2-Trimetilsilanil-etansulfonil)-2H-indazol-5-il]-propiónico



En una bolsa de guante que se sometió a 3 ciclo de purga de vacío/nitrógeno, en un matraz de reacción AIRFREE® (Schlenk) equipado con una barra de agitación se cargó con

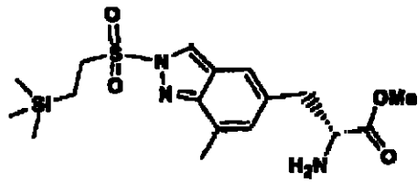
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trifluorometilsulfonato de (-)-1,2-bis((2R,5R)-2,5-dietilfosfolano)benceno(ciclooctadieno)rodio (I) (259 mg, 0.36 mmol, 9 mol-%), sellado con un septo de hule, y se removió de la bolsa de guante. El éster de metilo del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-il]-acrílico (2.03 g, 3.83 mmol) se pesaron en un segundo matraz de reacción AIRFREE (Schlenk) equipada con barra de agitación y sellado con un septo de hule. Después de 3 ciclos de purga de vacío/nitrógeno, esto se disolvió en metanol anhidro (80 mL, desoxigenado antes de la adición al burbujeo con nitrógeno durante al menos 1 h). Una vez en solución, esto se volvió a someter a 3 ciclos vacío/nitrógeno. La solución deshidroamino ácido se transfirió por medio de una cánula al matraz de reacción AIRFREE® (Schlenk) que contienen el catalizador. La mezcla de reacción se purgó con 5 ciclos de purga de vacío/hidrógeno antes de abrir el matraz a un globo de hidrógeno (1 atm). Después de 2.5 h, la mezcla de reacción se purgó con 3 ciclos de purga de vacío/nitrógeno. El solvente se evaporó y el residuo se sometió a cromatografía en columna (gradiente 1:4 acetato de etilo/hexanos para 1:2 acetato de etilo/hexanos) para dar 1.4 g (68%; ee = 99.2%) del compuesto del título como un sólido blanco. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 7.34 (s, 5H), 7.19 (s, 1H), 6.87 (s, 1H), 5.24 (d, J = 8.1 Hz,

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1H), 5.08 (dd, J = 18.3, 12.1 Hz, 2H), 4.67 (dd, J = 13.9, 6.2 Hz, 1H), 3.73 (s, 3H), 3.57-3.51 (m, 2H), 3.16 (dd, J = 14.0, 5.9 Hz, 1H). 3.06 (dd, J = 13.9, 6.6 Hz, 2.55 (s, 3H), 0.89-0.83 (m, 2H), 0.01 (s, 9H). ^{13}C-RMN ($CDCl_3$, 75 MHz) δ 172.0, 155.7, 151.7, 136.2, 132.2, 129.8, 129.5, 128.6, 128.4, 128.2, 125.1, 121.1, 118.1, 67.1, 54.7, 52.5, 51.1, 38.6, 17.1, 9.7, -2.0. Espectro de masa: 532 $(MH)^+$.

Éster de metilo del ácido (R)-2-Amino-3-[7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-il]-propiónico

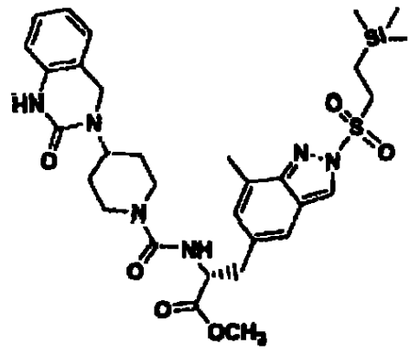


Éster de metilo del ácido 2-benciloxicarbonilamino-3-[7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-il]-propiónico (1.35 g, 2.54 mmol) y 10% paladio en carbono (135 mg) en metanol (40 mL) se agitaron durante 3.0 h bajo 55 psi (3.8665 kg/cm^2) hidrógeno usando un aparato Parr. La mezcla de reacción se purgó con 3 ciclos de purga de vacío/nitrógeno. La mezcla de reacción luego se filtró a través de una almohadilla de celite y la almohadilla se enjuagó con varias porciones de metanol. El metanol filtrado se evaporó para dar el compuesto del título (1.01 g, rendimiento cuantitativo) como una goma pegajosa. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 7.29 (s, 1H), 6.97 (s, 1H),

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3.79-3.73 (m, 1H), 3.73 (s, 3H), 3.56-3.50 (m, 2H), 5.12 (dd, J = 13.5, 5.12 Hz, 4.85 (dd, 13.5, 8.1 Hz, 1H), 2.58 (s, 3H), 0.87-0.81 (m, 2H), 0.01 (s, 9H). ^{13}C-RMN ($CDCl_3$, 75 MHz) δ 175.5, 151.8, 133.7, 129.9, 129.4, 125.0, 121.3, 117.9, 55.5, 52.1, 51.1, 41.4, 17.1, 9.8, -2.1. Espectro de masa: 398 $(MH)^+$.

Éster de metilo del ácido (R)-3-[7-Metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



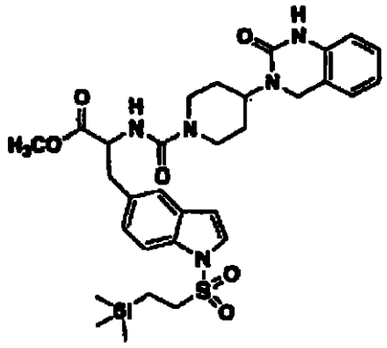
Una mezcla de éster de metilo del ácido 2-amino-3-[7-metil-2-(2-trimetilsilanil-etansulfonil)-2H-indazol-5-il]-propiónico (500 mg, 1.26 mmol) N,N-diisopropiletilamina (0.66 mL, 3.77 mmol) y disuccinimidilcarbonato (322 mg, 1.26 mmol) se agitaron junto con cloruro de metileno (20 mL) durante 30 min a temperatura ambiente. Luego, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (444 mg, 1.35 mmol) se agregó y la mezcla de reacción se dejo agitar durante la noche a temperatura

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ambiente. El solvente se evaporó y el residuo se sometió a cromatografía en columna instantánea (1:4 acetona/acetato de etilo) para dar 490 mg (60% de rendimiento) del compuesto del título como un sólido blanco. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.47 (s, 1H), 7.23 (s, 1H), 7.19-7.14 (m, 1H), 7.04 (d, J = 7.3 Hz, 1H), 6.97-6.93 (m, 2H), 6.77 (s, 1H), 6.65 (d, J = 7.7 Hz, 1H), 4.99 (d, J = 7.3 Hz, 1H), 4.81 (dd, J = 13.5, 6.2 Hz, 1H), 4.58-4.46 (m, 1H), 4.27 (s, 2H), 4.10-3.98 (m, 2H), 3.73 (s, 2H), 3.57-3.51 (m, 2H), 3.14-3.11 (m, 2H), 2.95-2.83 (m, 2H), 2.58 (s, 3H), 1.77-1.65 (m, 4H), 0.92-0.84 (m, 2H), -0.01 (s, 9H). Espectro de masa: 655 $(MH)^+$.

Preparado similarmente:

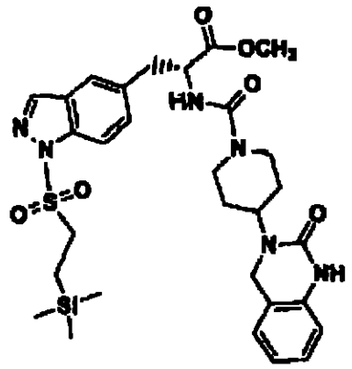
Éster de metilo del ácido (±)-2{[4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-propiónico



^{1}H-RMN (CD_3OD, 500 MHz) δ 7.85 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.27 (dd, J = 8.6, 1.5 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.95

(t, J = 6.79 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 3.7 Hz, 1H), 4.44-4.38 (m, 1H), 4.26 (s, 2H), 4.13-4.08 (m, 2H), 3.73 (s, 3H), 3.34-3.29 (m, 4H), 3.13 (dd, J = 13.5, 9.4 Hz, 2.89-2.79 (m, 2H), 1.76-1.70 (m, 1H), 1.63-1.59 (m, 3H), 0.76-0.72 (m, 2H), -0.07 (s, 9H); Espectro de masa: 640.40 $(MH)^+$.

Éster de metilo del ácido (R)-2-{[4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



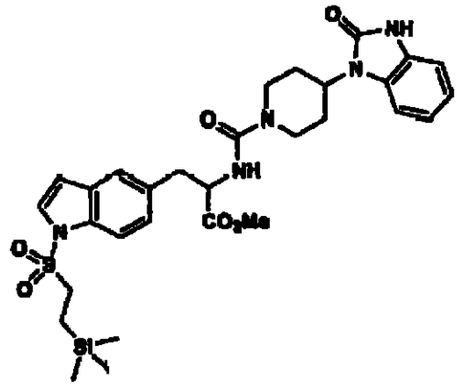
Una solución de éster de metilo del ácido (R)-2-Amino-3-[1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico (764 mg, 1.99 mmol), N,N-diisopropiletilamina (1.10 mL, 5.97 mmol) y disuccinimidilcarbonato (509 mg, 1.99 mmol) en cloruro de metileno (20 mL) se agitó durante 40 min a temperatura ambiente. Luego, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (70% puro, 703 mg, 2.13 mmol) se agregó y la mezcla de reacción se dejo agitar durante la noche a temperatura ambiente. El solvente se evaporó in vacuo y el residuo se sometió a cromatografía en columna instantánea (1:4

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acetona/acetato de etilo) para dar 1.15 g (90 %) del título del compuesto. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H)1, 6.76 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 5.01 (d, J = 7.6 Hz, 1H), 4.84 (dd, J = 13.1, 6.0 Hz, 1H), 4.56-4.49 (m, 1H), 4.28 (s, 2H), 4.13-3.98 (m, 2H), 3.73 (s, 3H), 3.39-3.35 (m, 2H), 3.28 (dd, J = 14.0, 6.1 Hz, 1H), 3.24 (dd, J = 13.7, 5.8 Hz, 1H), 2.94-2.87 (m, 2H), 1.75-1.67 (m, 4H), 0.91-0.87 (m, 2H), -0.02 (s, 9H). Espectro de masa: 641 $(MH)^+$.

Preparado similarmente:

Éster de metilo del ácido (±)-2-{[4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-propiónico

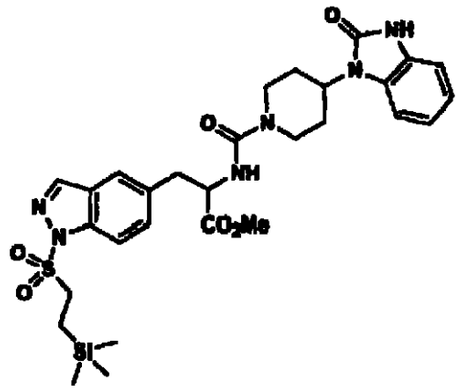


^{1}H-RMN (CD_3CN, 500 MHz) δ 9.78 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 7.49 (d, J = 3.7 Hz, 7.28 (dd, J = 8.5, 1.5 Hz, 7.10-7.08 (m, 1H), 7.05-7.03 (m, 1H), 6.99-6.97

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(m, 2H), 6.70 (d, J = 3.7 Hz, 1H), 5.91 (d J = 7.9 Hz, 1H), 4.66 (q, J = 8.2 Hz, 1H), 4.45-4.39 (m, 1H), 4.14 (br s, 3.68 (s, 3H), 3.36-3.32 (m, 2H), 3.27 (dd, J = 14.0, 5.5 Hz, 3.18 (dd, J = 13.7, 8.5 Hz, 1H), 2.90-2.84 (m, 2H), 2.55 (br s, 1H), 2.36-2.21 (m, 2H), 1.74-1.70 (m, 2H), 0.82-0.78 (m, 2H), -0.09 (s, 9H). Espectro de masa 626.26 $(MH)^+$.

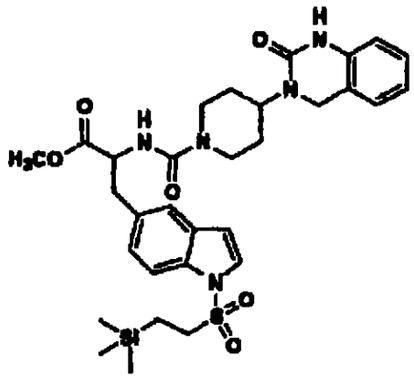
Éster de metilo del ácido (±)-2-{[4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



^{1}H-RMN (CD_3CN, 500 MHz) δ 9.61 (br s, 1H), 8. 35 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.51 (dd, J = 8.8, 1.5 Hz, 1H), 7.10-7.06 (m, 1H), 7.05-7.02 (m, 1H), 7.00-6.97 (m, 2H), 5.90n (d, J = 7.9 Hz, 1H), 4.67 4.62 (m, 1H), 4.42-4.36 (m, 1H), 4.13-4.07 (br s, 1H), 3.68 (s, 3H), 3.45-3.42 (m, 2H), 3.30 (dd, J = 14.0, 5.8 Hz, 1H), 3.20 (dd, J = 13.7, 8.8 Hz, 1H), 2.89-2.84 (m, 2H), 2.52 (br s, 1H), 2.33-2.23

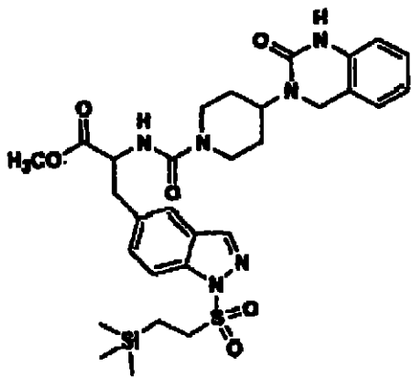
(m, 2H), 1.72-1.69 (m, 2H), 0.80-0.76 (m, 2H), -0.07 (s, 9H). Espectro de masa 627.25 $(MH)^+$.

Éster de metilo del ácido (±)-2-{[4-(2-Oxo-1,4-dihidro-2H-quinolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-propiónico



^{1}H-RMN (CD_3OD, 500 MHz) δ 7.85 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.51 (d, J = 3.7 Hz, 1H), 7.27 (dd, J = 8.6, 1.5 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 3.7 Hz, 1H), 4.44-4.38 (m, 1H), 4.26 (s, 2H), 4.13-4.08 (m, 2H), 3.73 (s, 3H), 3.34-3.29 (m, 4H), 3.13 (dd, J = 13.5, 9.4 Hz, 1H), 2.89-2.79 (m, 2H), 1.76-1.70 (m, 1H), 1.63-1.59 (m, 3H), 0.76-0.72 (m, 2H), -0.07 (s, 9H). Espectro de masa 640.40 $(MH)^+$.

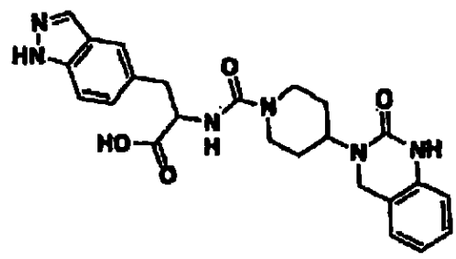
Éster de metilo del ácido (±)-2-{[4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



^{1}H-RMN (CD_3OD, 500 MHz) δ 8.39 (d, J = 0.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.75 (s, 1H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.14-7.10 (m, 2H), 6.94 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 4.63-4.60 (m, 1H), 4.43-4.37 (m, 1H), 4.27 (s, 2H), 4.11 (br s, 1H), 4.08 (br s, 1H), 3.71 (s, 3H), 3.47-3.43 (m, 2H), 3.37-3.33 (m, 1H), 3.18 (dd, J = 13.5, 10.0 Hz, 1H), 2.87-2.79 (m, 2H), 1.73-1.59 (m, 4H), 0.80-0.75 (m, 2H), -0.05 (s, 9H); ^{13}(CD_3OD, 125 MHz) δ 173.7, 155.5, 158.1, 141.0, 140.6, 137.2, 134.4, 131.3, 128.2, 126.1, 125.8, 122.2, 121.9, 118.3, 113.4, 112.6, 55.9, 52.1, 51.7, 50.8, 48.9, 48.6, 48.4, 48.2, 48.0, 47.9, 47.7, 47.5, 43.8, 43.7, 43.1, 37.2, 28.5, 9.8, -3.2. Espectro de masa: 641.40 $(MH)^+$.

Ejemplo 1

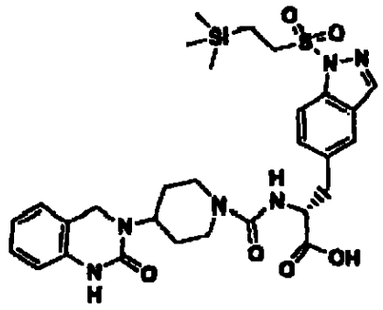
Ácido (±)-3-(1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Una solución de éster de tert-butilo del ácido 5-(2-etoxicarbonil-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-etil)-indazol-1-carboxílico (168 mg, 0.29 mmol) se disolvió en tetrahidrofurano (5 mL) en metanol (5 mL) se enfrió a 0°C. Una solución de monohidrato hidróxido de litio (49 mg, 2.04 mmol) en agua (5 mL) se agregó. La mezcla de reacción se agitó a 0°C durante 6 h y luego se colocó en el congelador durante unas 16 h adicionales. Los solventes se removieron in vacuo y el residuo se disolvió en agua (15 mL). El pH de la solución acuosa se ajustó a ca. 1 con 1N ácido clorhídrico. El precipitado sólido blanco resultante se recolectó por filtración. El sólido se secó bajo vacío para dar el compuesto del título (108 mg, 80%). ^{1}H-RMN (DMSO-d_6, 300 MHz) δ 12.94 (bs, 1H), 9.19

(s, 1H), 8.01 (s, 1H), 7.61 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 7.13-7.06 (m, 2H), 6.86 (t, J = 7.0 Hz, 1H), 6.76-6.72 (m, 2H), 4.32-4.24 (m, 2H), 4.09-4.02 (m, 4H), 3.17-2.97 (m, 2H), 2.72-2.59 (m, 2H), 1.57-1.35 (m, 4H). IR (KBr, cm^{-1}) 3424, 2963, 2930,1660, 1628, 1505, 1474, 1446, 753. Espectro de masa: 463 $(MH)^+$.

Ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico

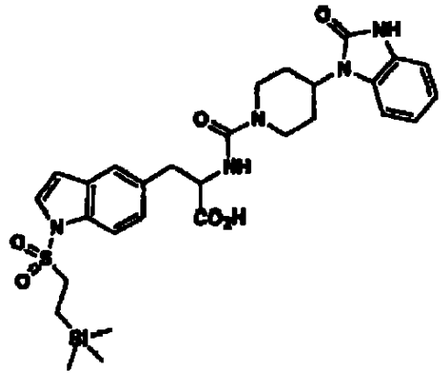


Una solución de éster de metilo del ácido (R)-2-{[4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico (775 mg, 1.21 mmol) en tetrahidrofurano (9 mL) y metanol (3 mL) se enfrió a 0°C. Una solución de monohidrato hidróxido de litio (115 mg, 4.84 mmol) en agua (3 mL) se agregó. La mezcla de reacción se agitó a 0°C durante 2 h y luego se colocó en el congelador a -15°C durante 16 h. Mientras se enfría la mezcla de reacción con un baño de

hielo, el pH se incrementó a ca. 7 por la adición de 1N ácido clorhídrico (3.8 mL). Los solventes orgánicos se removieron bajo vacío. La solución acuosa resultante se extrajo con acetato de etilo después de la adición de más ácido clorhídrico 1N (0.5 mL). Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron para dar 684 mg (90%) del compuesto del título como un sólido blanco. ^{1}H-RMN (DMSO-d_6, 300 MHz) δ 9.21 (s, 1H), 8.58 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.13-7.09 (m, 2H), 6.88-6.83 (m, 1H) 6.76-6.74 (m, 2H), 4.33-4.27 (m, 2H), 4.18 (s, 2H), 4.09-3.96 (m, 3H), 3.57-3.51 (m, 2H), 3.25-3.04 (m, 2H), 2.74-2.60 (m, 2H), 1.54-1.43 (m, 4H), 0.70-0.64 (m, 2H), -0.08 (s, 9H). Espectro de masa: 627 $(MH)^+$.

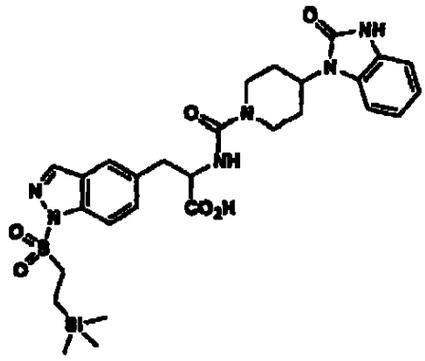
Preparado similarmente:

Ácido (±)-2-{[4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-il]-propiónico



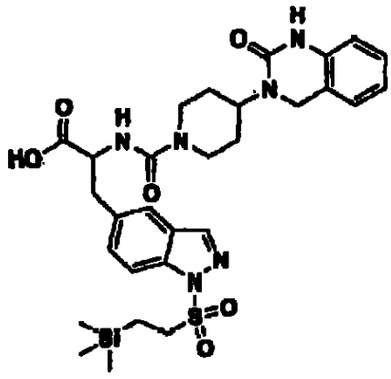
Espectro de masa 612.25 $(MH)^+$.

Ácido (±)-2-{[4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carbonil]-amino}-3-[1-(2-Trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico



Espectro de masa 613.26 $(MH)^+$.

Ácido (±)-2-{[4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico

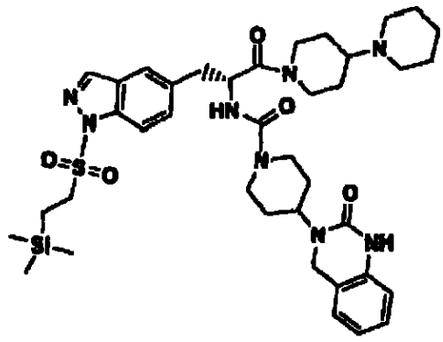


^{1}H-RMN (CD_3CN, 500 MHz) δ 8.37 (s, 1H), 8.08 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.53 (dd, J = 8.5,

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1.5 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.98 (td, j = 7.6, 1.2 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.28 (br s, 4.54-4.49 (m, 1H), 4.37-4.32 (m, 1H), 4.30 (s, 2H), 3.98-3.92 (m, 2H), 3.45-3.41 (m, 2H), 3.37 (dd, j = 14.0, 4.9 Hz, 1H), 3.20 (dd, J = 14.0, 9.7 Hz, 1H), 2.84-2.77 (m, 2H), 1.65-1.57 (m, 4H), 0.79-0.76 (m, 2H), -0.05 (s, 9H). Espectro de masa: 627.30 $(MH)^+$.

{2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (R)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxilico



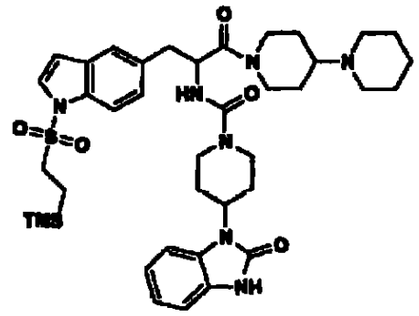
A una solución de ácido (R)-2-{[4-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico (554 mg, 0.88 mmol) y N,N-diisopropiletilamina (0.62 mL, 3.54 mmol) en cloruro de metileno (20 mL) se agregó una solución de 4-piperidinopiperidina (164 mg, 0.97 mmol) y PyBOP (460 mg, 0.88 mmol) en cloruro de metileno (15 mL). La mezcla de

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reacción se agitó durante 16 h a temperatura ambiente. Esto luego se concentró hasta aproximadamente 2 mL y se sometió a cromatografía en columna instantánea usando cloruro de metileno/metanol/trietilamina (94:5:1) como eluyente para dar 599 mg (87%) del compuesto del título como un sólido blanco. ^{1}H-RMN (CD_3CN, 300 MHz) δ 8.37 (s, 0.5H), 8.36 (s, 0.5H), 8.02-7.96 (m, 1H), 7.74 (s, 0.5H), 7.71 (s, 0.5H), 7.55-7.46 (m, 1H), 7.21-7.12 (m, 2H), 6.97-6.92 (m, 1H), 6.79 (d, J = 8.1 Hz, 1H), 5.71 (t, J = 8.1 Hz, 1H), 5.00 (dd, J = 15.0, 8.1 Hz, 1H), 4.63-4.51 (m 1H), 4.39-4.29 (m, 1H), 4.29 (s, 2H), 4.10-3.96 (m, 3H), 3.46-3.40 (m, 2H), 2.92-2.70 (m, 8H), 2.58-2.37 (m, 5H), 1.74-1.40 (m, 13H), 0.80-0.74 (m, 2H), -0.04 (s, 9H). Espectro de masa: 778 $(MH)^+$.

Preparado similarmente:

{2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico

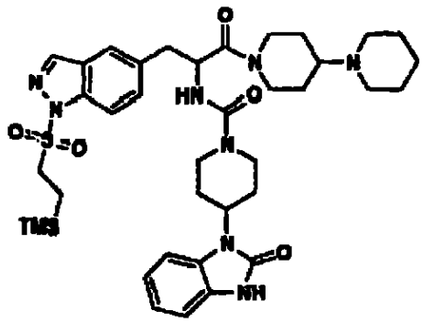


^{1}H-RMN (CD_3CN, 500 MHz) δ 9.42 (br s, 1H), 7.80 (d, J =

706 486

8.5 Hz, 0.6 H), 7.78 (d, J = 8.2 Hz, 0.4 H), 7.50 (s, 1H), 7.43 (t, J = 3.0 Hz, 1H), 7.27 (d, J = 8.5 Hz, 0.6 H), 7.23 (d, J = 8.5 Hz, 0.4 H), 7.10-7.07 (m, 1H), 7.02-6.95 (m, 3H), 6.69 (s, 0.4 H), 6.68 (s, 0.6 H), 5.88 (d, J = 8.5 Hz, 0.6 H), 5.85 (d, J = 8.4 Hz, 0.4 H), 5.04-4.98 (m, 1H), 4.49 (s, 0.4 H), 4.46 (s, 0.6 H), 4.36-4.30 (m, 1H), 4.11-4.07 (m, 1H), 3.97-3.91 (m, 1H), 3.31-3.28 (m, 2H), 3.11-3.05 (m, 6H), 2.87-2.80 (m, 2H), 2.43-2.07 (m, 8H), 1.78-1.74 (m, 4H), 1.71-1.65 (m, 2H), 1.46-1.40 (m, 2H), 1.37-1.31 (m, 2H), 0.80-74 (m, 2H), -0.10 (s, 9H). CL/EM: t_R = 2.47 min, 762.37 $(MH)^+$.

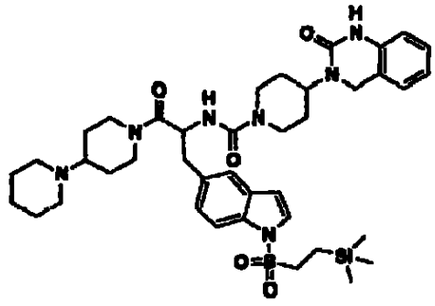
(2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3CN, 500 MHz) δ 9.67 (s, 1H), 8.32 (s, 1H), 7.96 (d, J = 8.7 Hz, 0.55 H), 7.93 (d, J = 8.6 Hz, 0.45 H), 7.70 (s, 1H), 7.51 (d, J = 8.6 Hz, 0.55 H), 7.47 (d, J = 8.8 Hz, 0.45 H), 7.08-7.05 (m, 1H), 7.03-6.99 (m, 1H), 6.98-6.94

(m, 2H), 6.01 (d, J = 7.9 Hz, 0. 45 H), 5.96 (d, J = 7.9 Hz, 0.55 h), 5.05-5.00 (m, 1H), 4.49-4.46 (m, 1H), 4.35-4.29 (m, 1H), 4.10-4.05 (m, 1H), 4.00-3.93 (m, 1H) 3.40-3.36 (m, 2H), 3.17-3.30 (m, 6H), 2.91-2.71 (m, 2H), 2.52-2.13 (m, 8H), 1.76 9br s, 4H), 1.69-1.65 (m, 2H), 1.44-1.41 (m, 2H), 1.34-1.30 (m, 2H), 0.77-0.71 (m, 2H), -0.08 (s, 9H). CL/EM: t_R = 2.35 min, 763.35 $(MH)^+$.

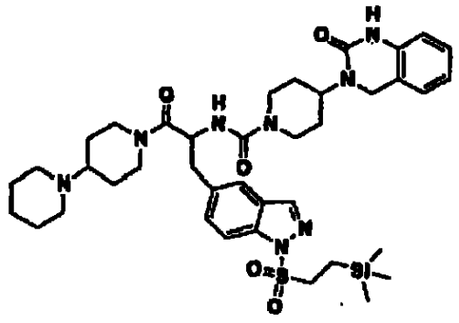
{2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3CN, 500 MHz) δ 8.17 (s, 0.6H), 8.16 (s, 0.4H), 7.84 (d, J = 8.5 Hz, 0.6 H), 7.81 (d, J = 8.5 Hz, 0.4 H), 7.54 (s, 0.4 H), 7.53 (s, 0.6H), 7.48 (t, J = 4.1 Hz, 1H), 7.31 (dd, J = 8.5, 1.5 Hz, 0.6 H), 7.28 (dd, 8.5, 1.5 Hz, 0.4 H), 7.18 (t, j = 7.4 Hz, 1H), 7.09-7.06 (m, 1H), 6.93 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 3.6 Hz, 6.09 (d, J = 8.2 Hz, 1H), 5.05-4.99 (m, 4.53-4.50 (m, 1H), 4.40-4.34 (m, 1H), 4.26 (s, 1.2H) < 4.24 (s, 0.8H), 3.99-3.94

(m, 1H), 3.35-3.30 (m, 2H), 3.15-3.07 (m, 3H), 3.08-3.03 (m, 1H), 2.81-2.73 (m, 3H), 2.55-2.37 (m, 6H), 2.21-2.16 (m, 1H), 2.13-2.08 (m, 1H), 1.69-1.57 (m, 4H), 1.51-1.45 (m, 4H), 1.41-1.35 (m, 4H), 0.83-0.74 (m, 2H), -0.06 (s, 9H). Espectro de masa: 776.44 $(MH)^+$.

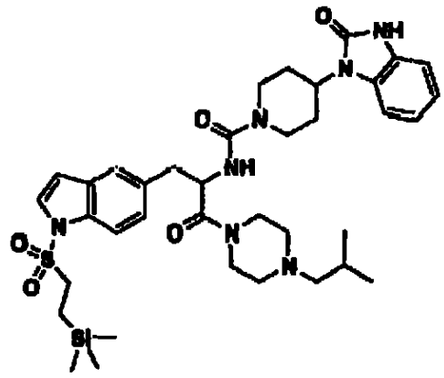
{2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Purificado por cromatografía en gel de sílice usando cloruro de metileno/trietilamina: (90:10:0.5) como eluyente. ^{1}H-RMN (CD_3CN, 500 MHz) δ 8.36 (s, 1H), 8.04 (s, 1H), 8.01 (d, J = 8.8 Hz, 0.6H), 7.97 (dd, J = 8.8 Hz, 0.4 H), 7.74 (s, 1H), 7.54 (dd, J = 8.5, 1.5 Hz, 0.6 H), 7.51 (dd, J = 8.5, 1.5 Hz, 0.4 H), 7.18 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 6.94 (t, J = 7.3 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.05 (d, J = 8.5 Hz, 0.4 H), 6.02 (d, J = 8.5 Hz, 0.6 H), 5.06-5.01 (m, 1H), 4.52-4.50 (m, 1H), 4.39-4.34 (m, 1H), 4.27 (s, 1.2 H), 4.25 (s, 0.8 H), 4.00-

3.97 (m, 2H), 3.45-3.40 (m, 2H), 3.20-3.08 (m, 2H), 2.81-2.74 (m, 2H), 2.56-2.39 (m, 8H), 2.27-2.24 (m, 1H), 2.20-2.16 (m, 1H), 1.68-1.57 (m, 4H), 1.52-1.45 (m, 4H), 1.34 (m, 4H), 1.06-1.01 (m, 0.80-0.75 (m, 2H), 0.07 (s, 9H). Espectro de masa: 777.40 $(MH)^+$.

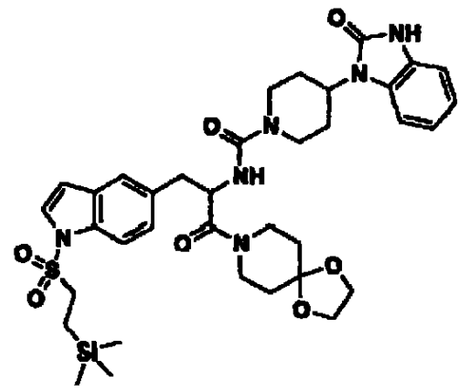
{2-(4-isobutil-piperazin-1-il)-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3CN, 500 MHz) δ 9.75 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.54 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.12-7.09 (m, 1H), 7.04-7.02 (m, 1H), 7.00-6.97 (m, 2H), 6.72 (d, J = 3.7 Hz, 1H), 5.97 (d, J = 8.2 Hz, 1H), 5.01 (dd, J = 14.6, 7.2 Hz, 1H), 4.40-4.34 (m, 1H), 4.15-4.08 (m, 2H), 3.58-3.54 (m, 1H), 3.50-3.45 (m, 2H), 3.39-3.35 (m, 1H), 3.36-3.32 (m, 2H), 3.14-3.10 (m, 8H), 2.89-2.83 (m, 2H), 2.34-2.23 (m, 4H), 2.17-2.13 (m, 1H), 0.85 (d, J = 6.7 Hz, 6H), 0.83-0.80 (m, 2H), -0.06 (s, 9H). Espectro de masa: 736.40 $(MH)^+$.

510 490

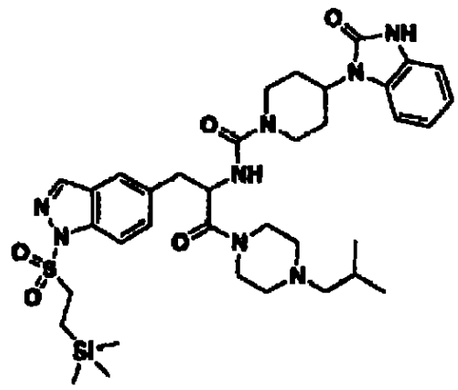
{2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3CN, 500 MHz) δ 9.27 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.55 (s, 1H), 7.48 (d, J = 3.6 Hz, 1H), 7.28 (dd, J = 8.5, 1.5 Hz, 1H), 7.13-7.10 (m, 1H), 7.06-7.03 (m, 1H), 7.01-6.98 (m, 2H), 6.72 (d, J = 3.6 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 5.05 (dd, J = 15.0, 7.3 Hz, 1H), 4.41-4.34 (m, 1H), 4.14-4.08 (m, 2H), 3.90-3.86 (m, 3H), 3.68-3.64 (m, 1H), 3.60-3.56 (m, 2H), 3.45-3.40 (m, 1H), 3.35-3.31 (m, 2H), 3.15 (dd, J = 13.4, 7.1 Hz, 1H), 3.05 (dd, J = 13.4, 7.0 Hz, 1H), 2.89-2.83 (m, 2H), 2.34-2.19 (m, 3H), 1.73-1.70 (m, 2H), 1.64-1.56 (m, 2H), 1.53-1.49 (m, 1H), 1.29-1.26 (m, 1H), 0.84-0.80 (m, 2H), 0.05 (s, 9H). Espectro de masa: 737.37 $(MH)^+$.

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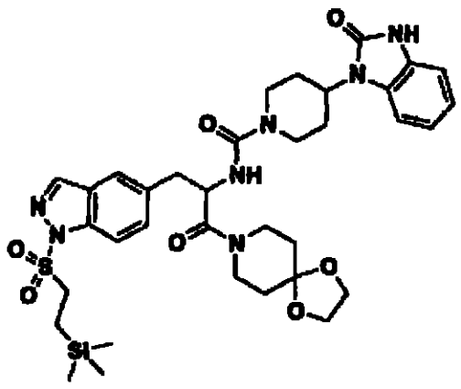
{2-(4-isobutil-piperazin-1-il)-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3CN, 500 MHz) δ 9.84 (s, 1H), 8.37 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J = 8.8, 1.5 Hz, 1H), 7.11-7.09 (m, 1H), 7.06-7.03 (m, 1H), 7.02-6.98 (m, 2H), 5.97 (d, J = 8.2 Hz, 1H), 5.02 (dd, J = 14.3, 7.3 hz, 1H), 4.39-4.33 (m, 1H), 4.14-4.07 (m, 2H), 3.53-3.50 (m, 3H), 3.46-3.42 (m, 2H), 3.45-3.39 (m, 1H), 3.20-3.06 (m, 2.89-2.83 (m, 2H), 2.30-2.27 (m, 4H), 2.21-2.17 (m, 1H), 1.74-1.70 (m, 3H), 0.86 (d, J = 6.7 Hz, 6H), 0.81-0.77 (m, 2H),- 0.04 (s, 9H). Espectro de masa: 737.40 $(MH)^+$.

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{2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico

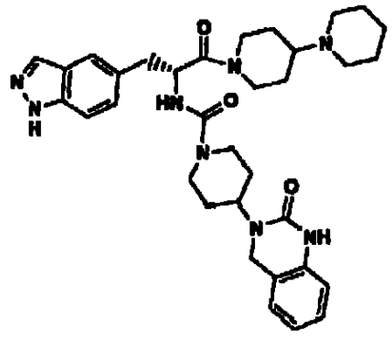


^{1}H-RMN (CD_3CN, 500 MHz) δ 9.34 (s, 1H), 8.36 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.11-7.08 (m, 1H), 7.06-7.03 (m, 1H), 7.02-6.98 (m, 2H), 5.98 (d, J = 8.2 Hz, 1H), 5.06 (dd, J = 14.6, 7.3 Hz, 4.39-4.32 (m, 1H), 4.13-4.03 (m, 2H), 3.92-3.88 (m, 2H), 3.71-3.66 (m, 1H), 3.63-3.53 (m, 2H), 3.48-3.45 (m, 1H), 3.44-3.40 (m, 2H), 3.19 (dd, j = 13.4, 6.5 Hz, 1H), 3.08 (dd, J = 13.7, 7.3 Hz, 1H), 2.85 (t, J = 12.8 Hz, 2H), 2.32-2.20 (m, 4H), 1.73-1.70 (m, 2H), 1.67-1.51 (m, 3H), 1.38-1.33 (m, 0.81-0.77 (m, 2H), -0.04 (s, 9H). Espectro de masa: 738.32 $(MH)^+$.

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Ejemplo 2

[2-[1,4']bipiperidinil-1'-il-1-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida () del ácido (R)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Una solución de (2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etnasulfonil)-1H-indazol-5-ilmetil]-etil)-amida del ácido (R)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (568 mg, 0.73 mmol) y fluoruro de cesio (1.11 g, 7.31 mmol) se calentó a 80°C en acetonitrilo (50 mL) durante 4.5 h. La mezcla de reacción se concentró y el residuo se sometió a cromatografía en columna instantánea (cloruro de metileno/metanol/trietilamina, 94:5:1) para dar 280 mg (63% de rendimiento) del compuesto del título como un sólido blanco con 98.2% ee como se determina por el análisis CLAR usando una columna Chiracel OD con 20% B (A = etanol, B = 0.05% dietilamina en hexanos) como eluyente (tiempo de

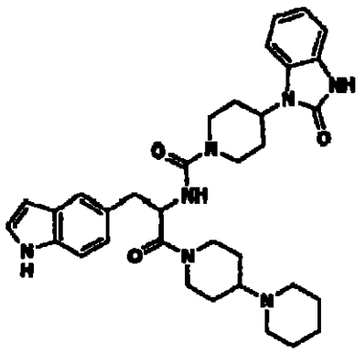
SP 494

retención : 9.51 min para el compuesto del título y 15.9 min para el enantiómero S). ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.04 (s, 0.75H), 8.03 (s, 0.25H), 7.67 (s, 0.75H), 7.65 (s, 0.25H), 7.56 (d, J = 8.5 Hz, 0.75H), 7.51 (d, J = 8.5 Hz, 0.25H), 7.41 (d, J = 8.5 Hz, 0.75H), 7.31 (d, J = 8.5 Hz, 0.25H), 7.19-7.12 (m, 2H), 6.97-6.94 (m, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.08-5.05 (m, 1H), 4.60-4.53 (m, 1H), 4.48-4.40 (m, 1H), 4.37 (s, 1.5H), 4.26 (s, 0.5H), 4.24-4.14 (m, 2H), 4.06-3.97 (m, 1H), 3.15 (d, J = 7.9 Hz, 1.5H), 3.12-3.05 (m, 0.5H), 2.94-2.86 (m, 3H), 2.57-2.51 (m, 1.5H), 2.47-2.42 (m, 1H), 2.37-2.33 (m, 0.75H), 2.03-2.02 (m, 1.5H), 1.87-1.75 (m, 3.75H), 1.73-1.68 (m, 2H), 1.67-1.54 (m, 3H), 1.53-1.44 (m, 4H), 1.43-1.34 (m, 2H), 1.30-1.26 (m, 1H), 0.83-0.77 (m, 0.75H), 0.16 hasta -0.24 (m, 0.75H). Espectro de masa: 613 $(MH)^+$.

Preparado similarmente:

Ejemplo 3

[2-[1,4']bipiperidinil-1'-il-1-(1H-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



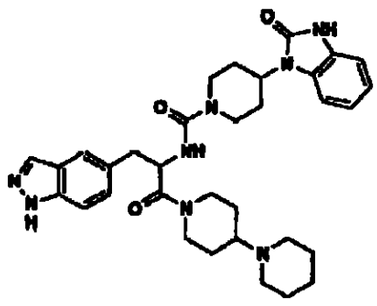
^{1}H-RMN (DMSO-d_6, 500 MHz) δ 10.99 (s, 0.6 H), 10.96 (s,

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0.4 H), 10.85 (s, 1H), 7.41 (s, 0.4H), 7.36 (s, 0.6H), 7.33 (d, J = 8.0 Hz, 0.6H), 7.29-7.26 (m, 1H), 7.16-7.14 (m, 1H), 7.10 (d, J = 7.6 Hz, 0.4 H), 7.02-6.96 (m, 4H), 6.81 (br s, 1H), 6.37-6.35 (m, 1H), 4.86 (q, J = 8.0 Hz, 0.6H), 4.80 (q, J = 7.5 Hz, 0.4 H), 4.45 (br s, 1H), 4.38-4.32 (m, 1H), 4.21-4.16 (m, 1H), 3.98 (br s, 1H), 3.18 (d, J = 5.2 Hz, 0.6H), 3.04-2.92 (m, 2.4 H), 2.82-2.74 (m, 4H), 2.37-2.33 (m, 2H), 2.25-2.08 (m, 4H), 2.04-1.90 (m, 2H), 1.47-1.24 (m, 10H), 0.75-0.71 (m, 1H). CL/EM: t_R= 1.90 min 598.42 $(MH)^+$.

Ejemplo 4

[2-[1,4']bipiperidinil-1'-il-1-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico

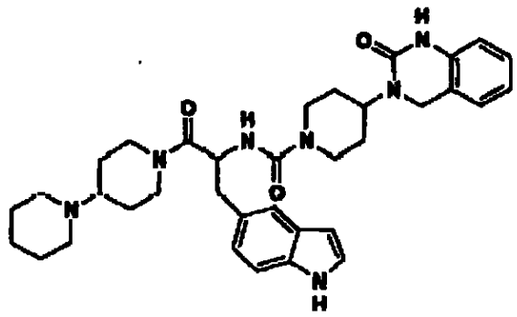


^{1}H-RMN (DMSO-d_6, 500 MHz) δ 10.70 (s, 1H), 8.22 (d, J = 8.2 Hz, 0.6H), 8.11 (s, 0.4H), 8.00 (s, 0.6H), 7.89 (d, J = 9.1 Hz, 0.4 H), 7.62-7.57 (m, 1H), 7.50-7.43 (m, 1H), 7.30-7.26 (m, 1H), 7.14-7.08 (m, 1H), 6.99-6.95 (m, 2H), 6.85 (br s, 1H), 4.89-4.80 (m, 1H), 4.45-4.31 (m, 2H), 4.18-4.00 (m,

2H), 3.26-3.16 (m, 1H), 3.09-2.96 (m, 2H), 2.82-2.73 (m, 4H), 2.38-2.34 (m, 2H), 2.24-2.08 (m, 4H), 2.03-1.88 (m, 2H), 1.47-1.22 (m, 10H), 0.90-0.84 (m, 1H). CL/EM: t_R= 1.73 min, 599.32 $(MH)^+$.

Ejemplo 5

[2-[1,4']bipiperidinil-1'-il-1-(1H-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



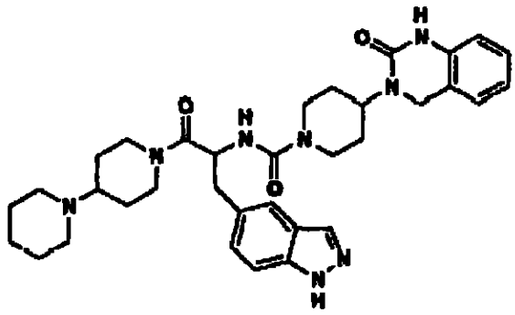
Una mezcla de (2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etnasulfonil)-1H-indol-5-ilmetil]-etil)-amida (52 mg, 0.067 mmol), fluoruro de cesio (51 mg, 0.33 mmol) en acetonitrilo (5 mL) se calentó a 80°C durante 4h. Los solventes se removieron in vacuo y el residuo se sometió a cromatografía en gel de sílice usando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido blanco (70% de rendimiento). ^{1}H-RMN (CD_3CN, 500 MHz) δ 9.30 (s, 1H), 7.48 (s, 1H), 7.42 (s, 1H), 7.39 (d, J = 8.2 Hz, 0.6H), 7.36 (d, J = 8.2 Hz, 0.4 H), 7.24-7.21 (m, 1H), 7.19 (t, J = 7.9 Hz, 7.12-7.09 (m, 1H), 7.06 (d,

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J = 8.2 Hz, 0.6 H), 7.02 (d, J = 8.2 Hz, 0.4 H), 6.95 (t, J = 7.4 Hz, 1, 4.04-3.93 (m, 1H), 3.07-3.02 (m, 1.6H), 2.95 (dd, J = 13.7, 7.1 Hz, 0.4 H), 2.85-2.72 (m, 3H), 2.56-2.37 (m, 3H), 2.42-2.37 (m, 1H), 1.99-1.95 (m, 7H), 1.76-1.51 (m, 8H), 1.45-1.40 (m, 3H). CL/EM: t_R: = 1.91 min, 612.44 $(MH)^+$.

Ejemplo 6

[2-[1,4']bipiperidinil-1'-il-1-(1H-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



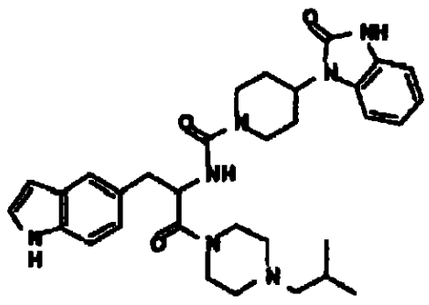
Purificado por cromatografía en gel de sílice usando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido blanco (90% de rendimiento). ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.04 (s, 0.7 H), 8.02 (s, 0.3 H), 7.67 (s, 0.7 H), 7.65 (s, 0.3H), 7.56 (d, J = 8.5 Hz, 0.7 H), 7.51 (d, J = 8.5 Hz, 0.3 H), 7.40 (d, J = 8.5 Hz, 0.7 H), 7.33 (d, J = 8.5 Hz, 0.3 H), 7.19-7.12 (m, 2H), 6.97-6.94 (m, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.08-5.05 (m, 1H), 4.59-4.54 (m ,1H),

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4.48-4.42 (m, 1H), 4.37 (s, 1H), 4.27-4.20 (m, 2H), 4.04 (d, J = 13.4 Hz, 0.3 H), 3.99 (d, J = 13.4 Hz, 0.7 H), 3.19-3.08 (m, 2H), 2.94-2.86 (m, 3H), 2.57 (br s, 2H), 2.51-2.36 (m, 2H), 2.07-2.05 (m, 1H), 1.90-1.31 (m, 16 H). CL/EM: t_R: 1.85 min, 613.44 $(MH)^+$. El enantiómero (R), cuya síntesis discreta se describe arriba (Ejemplo 1), se obtuvo por separación química del racemato al emplear las siguientes condiciones: columna prep. Chiracel OD, 50 x 500 mm, 20 um; A = EtOH, B= 0.05% dietilamina/hexano; 20% B @ 65 ml/min durante 45 min; tiempo de retención: 20.5 min para R y 32.8 min para enantiómeros S.

Ejemplo 7

[1-(1H-indol-5-ilmetil)-2-(4-isobutil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico

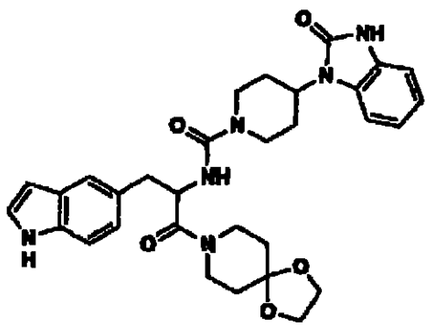


CL/EM: t_R: = 2.05 min, 572.31 $(MH)^+$.

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Ejemplo 8

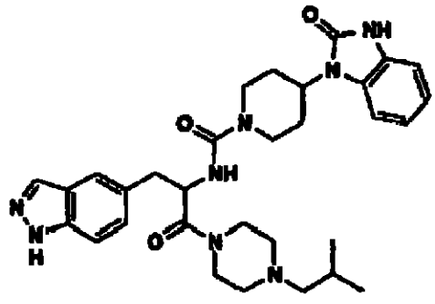
[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1H-indol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-Oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: t_R: = 2.35 min, 573.26 $(MH)^+$.

Ejemplo 9

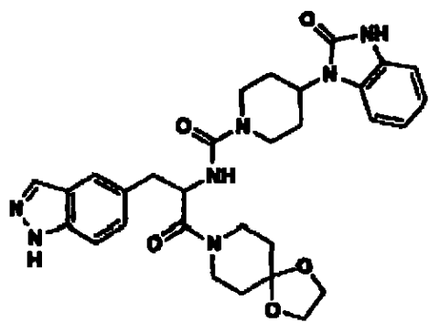
[1-(1H-indazol-5-ilmetil)-2-(4-isobutil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)piperidin-1-carboxílico



CL/EM: t_R= 1.86 min, 573.28 $(MH)^+$.

Ejemplo 10

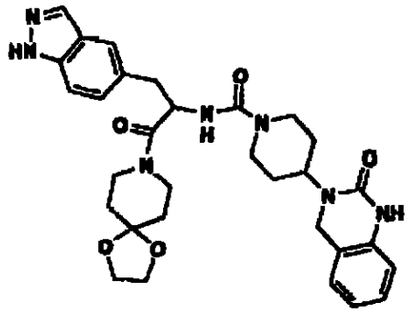
[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-(1H-indazol-5-ilmetil)-2-oxo-etil]amida del ácido (±)-4-(2-oxo-2,3-dihidro-benzoimidazol-1-il)-piperidin-1-carboxílico



CL/EM: t_R= 2.18 min, 574.23 $(MH)^+$.

Ejemplo 11

[2-(1,4-dioxa-8-aza-espiro[4.5]dec-8-il)-1-(1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

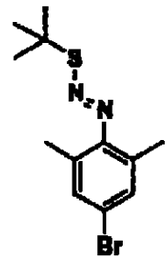


A una solución de ácido 3-(1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-

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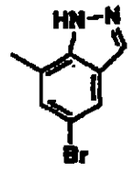
amino)-propiónico (95 mg, 0.21 mmol) y N,N-diisopropiletilamina (0.14 mL, 0.82 mmol) en dimetilformamida (5 mL) se agregó una solución de 1,4-dioxa-8-azaspiro[4,5]decano (32 mg, 0.23 mmol) y PyBOP (107 mg, 0.21 mmol) en cloruro de metileno (5 mL). La mezcla de reacción se agitó durante 16 h a temperatura ambiente. Todo solvente se removió usando alto vacío. El residuo se sometió a cromatografía en columna instantánea usando cloruro de metileno/metanol/trietilamina (93:5:2) para dar el compuesto del título como un sólido blanco (67 mg, 56% de rendimiento). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 10.52 (s, 1H), 7.97 (s, 1H), 7.54 (s, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 10.7 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.94 (t, J = 8.6 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 5.64 (d, J = 7.9 Hz, 1H), 5.16 (dd, J = 15.0, 6.7 Hz, 1H), 4.56-4.49 (m, 1H), 4.25 (s, 2H), 4.11 (br t, J = 15.6 Hz, 2H), 3.92-3.84 (m, 4H), 3.73-3.69 (m, 1H), 3.60-3.56 (m, 1H), 3.48-3.43 (m, 1H), 3.22-3.17 (m, 1H), 3.11 (d, J = 6.7 Hz, 2H), 2.90-2.85 (m, 2H), 2.68-2.60 (m, 4H), 1.67-1.61 (m, 2H), 1.54-1.49 (m, 2H). Espectro de masa: 588 $(MH)^+$.

Sulfuro de 4-bromo-2,6-dimetilfenildiazo-t-butilo



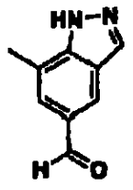
4-Bromo-2,6-dimetilanilina (20.00 g, 100 mmol) se muele hasta un polvo con un mortero y luego se suspendió en 24% de ácido clorhídrico (41 mL). La mezcla agitada se enfrió hasta -20°C y se trató con nitrito de sodio (7.24 g, 1. 05 equiv) en agua (16 mL), gota a gota durante 40 min mientras la temperatura se mantiene debajo de -5°C. Después de unos 30 min adicionales a -5°C hasta -20°C, la mezcla se amortigua hasta ca. pH 5 con acetato de sodio sólido. Esta mezcla (mantenido a ca. -10°C) se agregó en porciones a una solución agitada de t-butil tiol (11.3 mL, equiv) en etanol (100 mL) a 0°C durante ca. 10 min. Después de la adición, la mezcla se agitó a 0°C durante 30 min y luego se agregó hielo molido (ca. 150 mL). La mezcla se almacena en el refrigerador durante la noche. El sólido café ligero resultante se recolectó por filtración, se lavó con agua, y se secó bajo alto vacio durante varias h. (26.90 g, 89%). El compuesto aparenta ser estable como un sólido pero se siguió la descomposición significante cuando se alcanzó la recristalización del etanol. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.58 (9H, s), 1.99 (6H, s), 7.21 (2H, s). Espectro de masa: 303.05 $(MH)^+$.

5-Bromo-7-metilindazol



En un matraz de fondo redondo secado a la flama, sulfuro 4-bromo-2,6-dimetilfenildiazo-t-butilo (12.50 g, 41.5 mmol) y t-butóxido de potasio (46.56 g, 10 equiv) se combinaron. Una barra de agitación se agregó y la mezcla se colocó bajo nitrógeno. A esto se agregó DMSO seco (120 mL). La mezcla se agitó vigorosamente durante la noche a ta. La mezcla de reacción luego se vacío cuidadosamente en una mezcla de hielo molido (400 mL) y 10% ácido clorhídrico (200 mL). La suspensión resultante se dejó colocado a 4°C durante la noche y el sólido se recolectó por filtración y se lavó con agua. El sólido crudo se disolvió en 5:1 y cloruro de metileno/metanol y la solución se secó sobre sulfato de magnesio y se evaporó para dar el producto como un sólido completamente blanco (7.60 g, 87%). ^{1}H-RMN ($CDCl_3/CD_3OD$, 500 MHz) δ 2.51 (3H, s), 7.22 (1H, s), 7.69 (1H, s), 7.94 (1H, s). Espectro de masa: 211.03 $(MH)^+$.

7-metilindazol-5-carboxaldehído



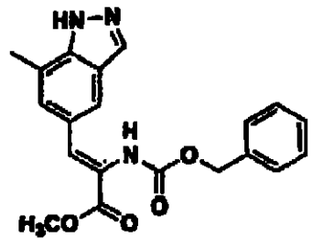
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5-Bromo-7-metilindazol (6.10 g, 28.9 mmol) e hidruro de sodio (60% en aceite mineral, 1.27 g, 1.1 equiv) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se agregó tetrahidrofurano seco (30 mL). La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante el cual se volvió homogénea. La mezcla agitada se enfrió a -70°C y se agregó una solución de sec-butillitio en ciclohexano (1.4M, 45 mL, 2.2 equiv) durante varios minutos. Después de 1 h se agregó dimetilformamida (10 mL) durante varios minutos. La mezcla se permitió calentar a temperatura ambiente y se agitó durante la noche. Esto luego se enfrió a 0°C y se trató cuidadosamente con 1N ácido clorhídrico (60 mL). Después de pocos minutos, el bicarbonato de sodio sólido se agregó para hacer básica la mezcla a pH 9-10. Las capas se separaron y la fase acuosa se lavó 2 veces con acetato de etilo. Las fases orgánicas combinadas se extrajeron con 0.8M sulfato ácido de sodio (3 x 125 mL). Las fases acuosas combinadas se lavaron con acetato de etilo (100 mL) y luego el pH se ajustó a ca. 10 con hidróxido de sodio sólido. La suspensión resultante se extrajo con acetato de etilo (3 x 150 mL). Las fases orgánicas combinadas se lavaron con salmuera, se secó (sulfato de magnesio) y se evaporaron para dar el producto

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como un sólido marrón ligero (3.01 g, 65%). ^{1}H-RMN ($CDCl_3$, MHz) δ 2.63 (3H, s), 7.73 (1H, s), 8.12 (1H, s), 8.25 (1H, s), 10.03 (1H, s). Espectro de masa: 161.06 $(MH)^+$.

Éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-metil-1H-indazol-5-il)-acrílico

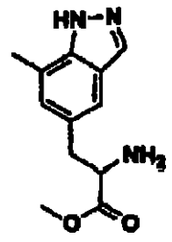


Una solución agitada de éster de trimetilo de N-benciloxicarbonil-α-fosfonoglicina (5.51 g, 1.2 equiv.) en tetrahidrofurano (30 mL) a temperatura ambiente se trató con tetrametilguanidina (1.91 mL, 1.1 equiv). Después de 10 min, se agregó 7-metilindazol-5-carboxaldehído (2.22 g, 13.86 mmol) en tetrahidrofurano (20 mL). La desaparición del material de partida se monitoreó por TLC y CL/EM. Después de 5 días a temperatura ambiente, el solvente se evaporó y el residuo se disolvió en acetato de etilo. La solución se lavó con 2% de ácido fosfónico y salmuera, se secó (sulfato de magnesio) y se evaporó. El residuo se purificó por cromatografía instantánea en gel de sílice, eluído con 1) 1:1 y 2) 2:1 acetato de etilo/hexano, para dar el producto como

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una espuma incolora (4.93 g, 97%). ^{1}H-RMN ($CDCl_3$, MHz) δ 2.43 (3H, s), 3.80 (3H, s), 5.12 (2H, s), 6.66 (1H, s), 7.28 (5H, brs), 7.33 (1H, s), 7.47 (1H, s), 7.74 (1H, s), 7.96 (1H, s). Espectro de masa: 366.16 $(MH)^+$.

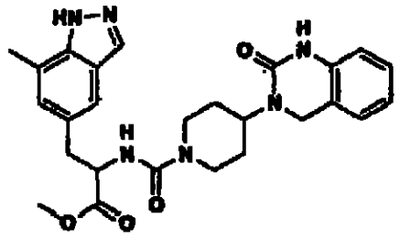
Éster de metilo del ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propiónico



Una solución de éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-metil-1H-indazol-5-il)-acrílico (4.93 g, 13.49 mmol) en metanol (125 mL) se desgasificó al burbujear el nitrógeno a través de durante 30 min y luego se agregó cuidadosamente 10% paladio en carbón mineral (0.6 g). La mezcla se hidrogenó a 40 psi (2.81 kg/cm^2) en un aparato de agitación Parr durante la noche. El catalizador se removió por filtración a través de una almohadilla de celite y el filtrado se concentró in vacuo para dar el producto como una espuma incolora (3.62 g, cuant.). ^{1}H-RMN (CD_3OD, 500 MHz) δ 2.45 (3H, s), 2.99 (1H, Abq), 3.22 (1H, Abq), 3.74 (3H, s), 3.89 (1H, m), 6.91 (1H, s), 7.31 (1H, s), 7.73 (1H, s). Espectro de masa: 234.11 $(MH)^+$.

Ejemplo 12

Éster de metilo del ácido (±)-3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

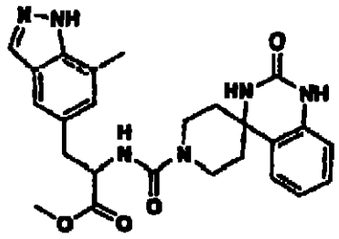


Una solución agitada de éster de metilo del ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propiónico (162.9 mg, 0.698 mmol) en cloruro de metileno (3 mL) a temperatura ambiente se trató con carbonil diimidazol (113.2 mg, 1 equiv). Después de 1.5 h a temperatura ambiente, se agregó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (161.5 mg, 1 equiv.). La mezcla se agitó a temperatura ambiente durante la noche. Un precipitado blanco tiene la forma que se muestra para ser el producto deseado. El solvente se evaporó y el residuo triturado con cloruro de metileno. El producto se recolectó por filtración, se lavó con cloruro de metileno y se secó in vacuo para dar un sólido blanco (241.5 mg, 71%). Algo de producto restante los licores madre. ^{1}H-RMN (dimetilformamida-d_7, 500 MHz) δ 1.75 (4H, m), 2.78 (3H, s), 2.7-3.1 (4H, m), 3.35 (2H, m), 3.86 (3H, s), 4.44 (2H, s), 4.57 (1H, m), 4.72 (1H, m), 7.11 (3H, 7.31 (1H, s), 7.34 (2H, m), 7.72 (1H, s), 9.34 (1H, s). Espectro de masa: 491.13 $(MH)^+$.

Preparado similarmente:

Ejemplo 13

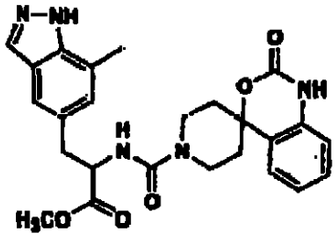
Éster de metilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolin)carbonil amino]-propiónico



^{1}H-RMN (DMSO-d_6) δ 1.59 (4H, m), 2.46 (3H, s), 3.00-3.08 (4H, m), 3.6 (3H, s), 3.78-3.81 (2H, m), 4.30-4.32 (1H, m), 6.78-6.88 (4H, m), 7.03 (1H, s), 7.10 (1H, m), 7.13 (1H, s), 7.41 (1H, s), 7.96 (1H, s), 9.12 (1H, s). Espectro de masa: 477.11 $(MH)^+$.

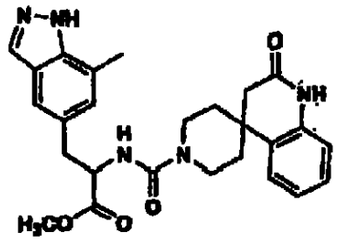
Ejemplo 14

Éster de metilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-(1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazin-4'4-piperidin-carbonilamino)-propiónico



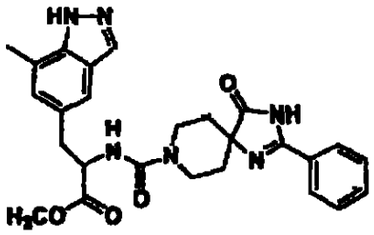
Espectro de masa: 478.15 $(MH)^+$.

Éster de metilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{3',4'-dihidro-2'-oxoespiro-(piperidin-4-4'-(1H)-quinolincarbonilo



^{1}H-RMN (DMSO-d_6) δ 1.42-1.56 (4H, m), 2.47 (3H, s), 2.50-2. 54 (1H, d), 2.60-2.64 (1H, d), 2.98-3.06 4H, m), 3.60 (3H, s) 3.80 (2H, m), 4.30 (1H, m), 6.86 (2H, d), 6.95 (2H, m), 7.15 (1H, m), 7.40 (1H, s), 7.95 (1H, s), 8.32 (1H, s), 10.14 (1H, s), 13.05 (1H, s). Espectro de masa: 476.17 $(MH)^+$.

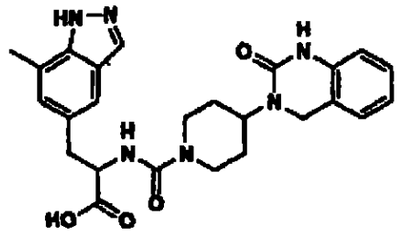
Éster de metilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-[2'-fenil-1',3',8'-triaza-espiro(4',5')carbonil amino]-propiónico



^{1}H-RMN (DMSO-d_6) δ 1.50 (2H, m), 1.68 (2H, m), 2.46 (3H, s se traslapó con DMSO), 3.05 (2H, m), 3.30 (2H, m), 3.60 (3H, s), 3.86 (2H, m), 4.28 (1H, m), 6.98 (1H, d), 7.04 (1H, s), 7.40 (1H, s), 7.58 (2H, m), 7.65 (1H, m), 8.00 (1H, s), 8.04 (2H, m). Espectro de masa: 489.15 $(MH)^+$.

Ejemplo 15

Ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

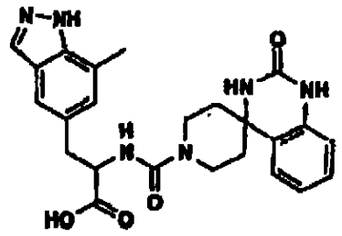


Una suspensión de éster de metilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (240.0 mg, 0.489 mmol) en 1:1 tetrahidrofurano/metanol (20 mL) a temperatura ambiente se trató con una solución de hidróxido de litio (140.5 mg, 7 equiv) en agua (10 mL). Dentro de 1 min, la mezcla se volvió homogénea y esto se colocó para mantenerse a 4°C durante la noche. Los solventes se evaporaron a ca. 30°C y el pH se ajustó a ca. con 1N de ácido clorhídrico. La suspensión blanca resultante se almacenó a 4°C durante varias horas y el producto se recolectó por filtración, se lavó con una cantidad pequeña de agua, y se secó in vacuo (169.0 mg, 73%). El cloruro de sodio sólido se agregó al filtrado resultante en precipitación de más producto (5.2 mg, rendimiento total de 75%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.2-1.7 (4H, m), 2.58 (3H, s), 2.5-3.2 (4H, m), 3.35 (2H, m), 4.15 (2H, m), 4.36 (1H, m), 4.60 (1H, m), 6.79 (1H, d), 6.96 (1H,

t), 7.18 (3H, m), 7.49 (1H, s), 8.00 (1H, s). Espectro de masa: 477.13 $(MH)^+$.

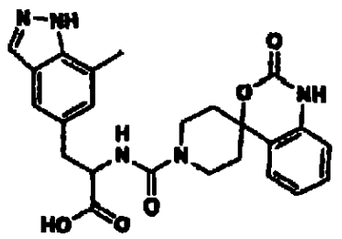
Preparado similarmente:

Ácido 3-(7-Metil-1H-indazol-5-il)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolincarbonil amino]-propiónico



^{1}H-RMN (DMSO-d_6) δ 1.58 (4H, m), 2.46 (3H, s), 3.00-3.23 (3H, m), 3.78-3.91 (3H, m), 3.88 (2H, m) 4.28 (1H, s), 6.70 (1H, d), 6.75-6.85 (3H, m), 7.04 (1H, d), 7.11 (1H, m) 7.18 (1H, s), 7.96 (1H, s), 13.02 (1H, m). Espectro de masa: 463.09 $(MH)^+$.

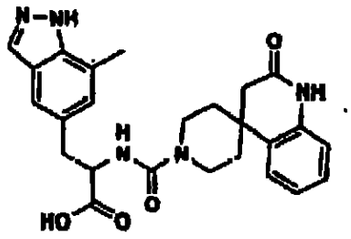
Éster de metilo del ácido 3-(7-metil-1H-indazol-5-il)-2-(1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazin-4'4-piperidin-carbonilamino)-propiónico



BB512

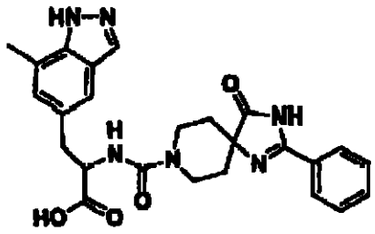
^{1}H-RMN (DMSO-d_6) δ 1.63-1.98 (4H, m), 2.46 (3H, s, 7-Me se traslapó con DMSO), 2.98-3.32 (4H, m), 3.90 (2H, m), 4.28 (1H, m), 6.78 (1H, d), 6.87 (2H, m), 6.96 (1H, m), 7.05 (1H, s), 7.24 (1H, m), 7.41 (1H, s), 7.96 (1H, s), 10.22 (1H, s) 12.42 (1H, br.) 13.02 (1H, m). Espectro de masa: 464.07 $(MH)^+$.

Ácido 3-(7-Metil-1H-indazol-5-il)-2{3',4'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinolin-carbonil amino}-propiónico



^{1}H-RMN (DMSO-d_6) δ 1.39-1.45 (2H, m), 1.53-1.56 (2H, m), 2.46 (3H, s), 2.50-2.54 (1H, d), 2.60-2.63 (1H, d), 2.88-3.00 (3H, m), 3.09-3.11 (1H, m), 3.78-3.81 (2H, m), 4.27 (1H, m), 6.69-6.70 (1H, d), 6.86-6.87 (1H, d), 6.93-6.94 (1H, m) 6.99-7.00 (1H, m), 7.05 (1H, m), 7.41 (1H, s), 7.95 (1H, s), 10.13 (1H, s), 12.50 (1H, m), 13.03 (1H, m). Espectro de masa: 462 $(MH)^+$.

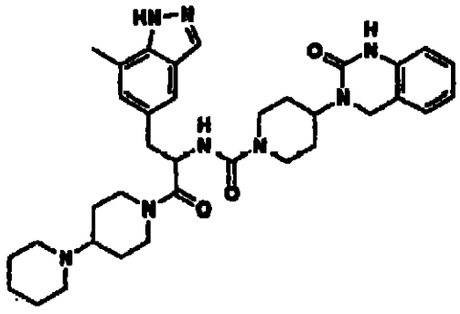
Ácido 3-(7-Metil-1H-indazol-5-il)-2-[2'-fenil-1',3',8'-triaza-espiro(4',5')deo-1-ene-8-crbonil amino]-propiónico



^{1}H-RMN (DMSO-d_6) δ 1.36 (2H, m), 1.63 (2H, m), 2.46 (3H, s se traslapó con DMSO), 2.98-3.03 (2H. m), 3.09-3.11 (2H, m), 3.86 (2H, m), 4.21 (1H, m), 6.69 (1H, m), 7.04 (1H, s), 7.40 (1H, s), 7.52-7.58 (3H, m), 7.99 (3H, m), 11.55 (1H, m), 13.00 (1H, m). Espectro de masa: 475.08 $(MH)^+$.

Ejemplo 16

[2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Una solución agitada de ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

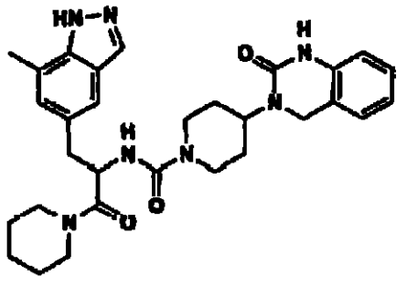
224 514

carbonil]-amino}-propiónico (65.7 mg, 0.138 mmol) en 2:1 dimetilformamida/cloruro de metileno (1.5 mL) a 0°C se trató con 4-(1-piperidil)-piperidina (46.5 mg, 2 equiv), diisopropiletilamina (0.048 mL, 2 equiv) y PyBOP® (75.5 mg, 1.05 equiv). El baño de hielo se permite que se funda y la mezcla se agitó a temperatura ambiente durante la noche. Los solventes se removieron bajo alto vacío y el residuo se purificó por cromatografía instantánea en gel de sílice, eluído con 18:1 cloruro de metileno/metanol que contienen 1% trietilamina, para dar el producto como un sólido amarillo pálido (80.4 mg, 93%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 0.28 (1H, m), 0.75 (1H, m), 1.2-2.0 (12H, m), 2.08 (2H, m), 2.4-2.5 (3H, m), 2.59 (3H, s), 2.68 (2H, m), 2.90 (4H, m), 3.08 (4H, m), 3.9-5.1 (4H, varias m), 6.81 (1H, d), 6.96 (1H, t), 7.16 (3H, m), 7.49 (1H, s), 8.03 (1H, s). Espectro de masa: 627.29 $(MH)^+$.

Preparado similarmente:

Ejemplo 17

[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2piperidin-1-il-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

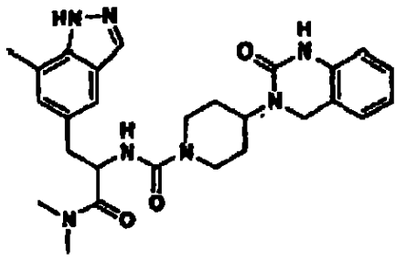


LF 515

^{1}H-RMN (CD_3OD, 500 MHz) δ 0.87 (1H, m), 1.33 (1H, m), 1.47 (2H, m), 1.80 (6H, m), 2.57 (3H, s), 2.89 (2H, m), 3.06 (2H, m), 3.18 (4H, m), 3.40 (2H, m), 3.61 (1H, m), 4.16 (1H, m), 4.28 (1H, Abq), 4.43 (1H, m), 5.02 (1H, m), 6.51 (1H, d), 6.79 (1H, d), 6.96 (1H, t), 7.11 (1H, d), 7.15 (1H, t), 7.48 (1H, s), 8.01 (1H, s). Espectro de masa: 544.24 $(MH)^+$.

Ejemplo 18

[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

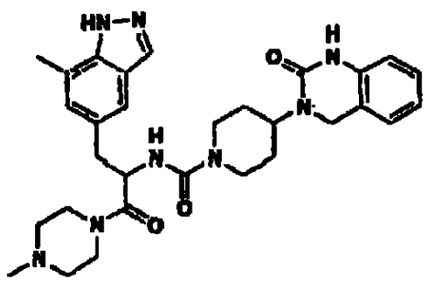


^{1}H-RMN (CD_3OD, 500 MHz) δ 1.12 (2H, d), 1.64 (2H, m), 2.57 (3H, s), 2.74 (1H, m), 2.87 (3H, s), 2.89 (3H, s), 2.86 (2H, m), 3.07 (2H, m), 3.20 (1H, m), 4.17 (1H, m), 4.25 (1H, Abq), 4.43 (1H, m), 4.97 (1H, m), 6.79 (1H, d), 6.95 (1H, t), 7.0-7.4 (3H, m), 7.48 (1H, d), 8.01 (1H, s). Espectro de masa: 504.15 $(MH)^+$.

516

Ejemplo 19

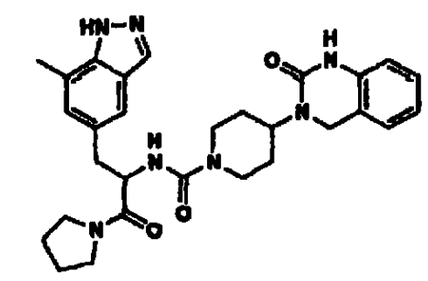
[1-(7-metil-1H-indazol-5-ilmetil)-2-(4-metil-piperazin-1-il)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3OD, 500 MHz) δ 1.30 (2H, m), 1.66 (2H, m), 1.78 (1H, m), 1.90 (1H, m), 2.00 (3H, s), 2.19 (1H, m), 2.35 (1H, m), 2.58 (3H, s), 2.88 (2H, m), 3.09 (2H, d), 3.10-3.45 (3H, m), 3.66 (1H, m), 4.19 (2H, d), 4.20 (2H, s), 4.43 (1H, m), 4.98 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.11 (2H, m), 7.16 (1H, t), 7.47 (1H, s), 8.02 (1H, s). Espectro de masa: 559.23 $(MH)^+$.

Ejemplo 20

[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-pirrolidin-1-il-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

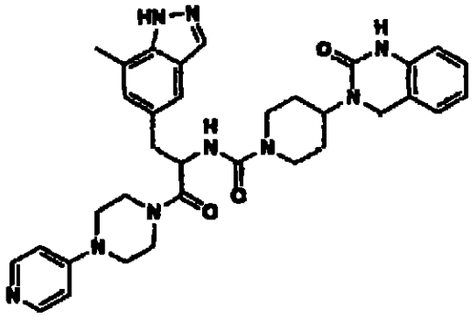


PTP 517

^{1}H-RMN (CD_3OD, 500 MHz) δ 1.40-1.90 (5H, m), 2.02 (3H, brs), 2.57 (3H, s), 2.86 (1H, m), 2.89 (2H, q), 3.09 (2H, m), 3.16 (1H, m), 3.25 (2H, m), 3.40 (1H, m), 3.56 (1H, m), 4.17 (2H, d), 4.27 (2H, s), 4.40 (1H, m), 4.69 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.10 (1H, s), 7.16 (1H, m), 7.48 (1H, s), 7.53 (1H, m), 8.01 (1H, s). Espectro de masa: 530.19 $(MH)^+$.

Ejemplo 21

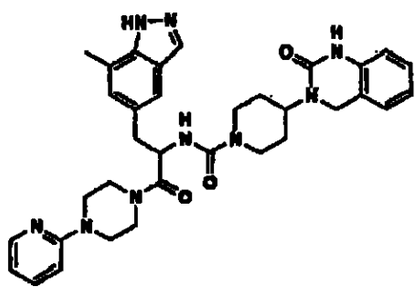
[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3OD, 500 MHz) δ 1.38 (1H, t), 1.68 (2H, m), 1.81 (1H, m), 2.30 (1H, m), 2.53 (3H, s), 2.95 (4H, m), 3.13 (2H, d), 3.22 (1H, m), 3.35-3.65 (4H, m), 3.79 (1H, m), 4.18 (2H, d), 4.31 (2H, s), 4.42 (1H, m), 4.99 (1H, t), 6.64 (2H, d), 6.80 (1H, d), 6.89 (1H, m), 6.96 (1H, t), 7.14 (3H, m), 7.51 (1H, s), 7.99 (1H, s), 8.10 (2H, d), 8.16 (1H, m). Espectro de masa: 622.26 $(MH)^+$.

Ejemplo 22

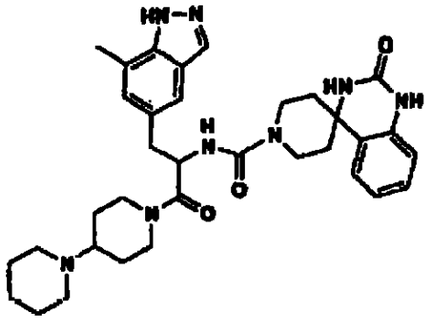
[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-(4-piridin-2-il-piperazin-1-il)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



^{1}H-RMN (CD_3OD, MHz) δ 1.27 (1H, m), 1.38 (1H, m), 1.67 (2H, m), 1.84 (1H, m), 2.54 (3H, s), 2.65 (1H, m), 2.88 (2H, m), 3.15 (4H, m), 3.35 (1H, m), 3.58 (3H, m), 3.77 (1H, m), 4.18 (2H, d), 4.30 (2H, s), 4.42 (1H, m), 5.01 (1H, t), 6.62 (1H, d), 6.70 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.10 (3H, m), 7.50 (1H, s), 7.54 (1H, t), 7.99 (1H, s), 8.05 (1H, 7). Espectro de masa: 622.25 $(MH)^+$.

Ejemplo 23

(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolin]-1-carboxamida

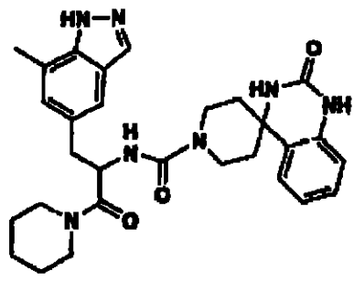


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^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.2-1.73 (14H, m), 2.46 (3H, s), 2.75-3.24 (12H, m), 3.87 (2H, m), 4.45 (1H, m), 4.78-4.85 (1H, m), 6.80 (1H, m), 6.86 (1H, m), 7.05 (1H, m), 7.12 (1H, m), 7.21 (1H, m), 7.27 (2H, m), 7.98 (1H, m), 9.23 (1H, m). Espectro de masa: 613.25 $(MH)^+$.

Ejemplo 24

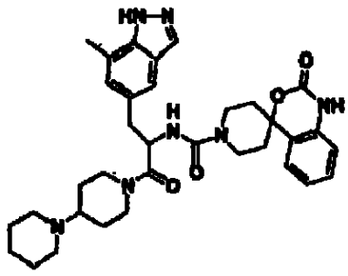
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-(1-piperidinil)-2-oxoetil]-2'-3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolin]-1-carboxamida



^{1}H-RMN (CD_3OD, 500 MHz) δ 0.87 (1H, m), 1.28-1.47 (5H, m), 1.74-1.85 (4H, m), 2.53 (3H, s), 3.02-3.38 (8H, m), 3.92 (2H, m), 5.02 (1H, m), 6.82 (1H, d), 6.99 (1H, d), 7.04-7.09 (2H, m), 7.17 (1H, m), 7.32 (2H, s), 7.45 (1H, s), 7.96 (1H, s). Espectro de masa: 530.17 $(MH)^+$.

Ejemplo 25

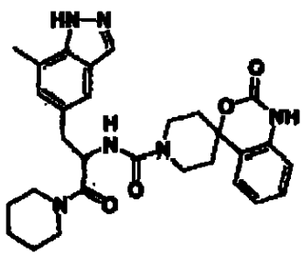
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-1',2'-dihidro-2'--oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida



^{1}H-(DMSO-d_6, 500 MHz) δ 1.88 (14H, m), 2.64 (3H, s), 2.78 (12H, m), 4.0 (2H, m), 4.4 (1H, m), 4.85 (1H, m), 6.80-6.88 (2H, m), 7.03 (2H, m), 7.11 (1H, m), 7.23 (1H, m), 7.36 (2H, m), 7.97 (1H, m). Espectro de masa: 614.73 $(MH)^+$.

Ejemplo 26

(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-(1-piperidinil)-2-oxoetil]-1',2'-dihidro-2'—oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida

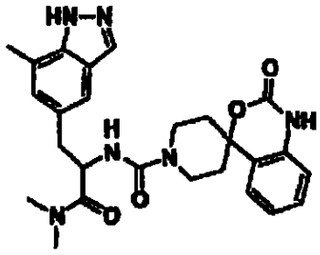


^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.15-1.91 (10H, m), 2.47 (3H,

s), 2.95-3.05 (6H, m) 3.40 (4H, m) 3.95 (2H, d), 4.81 (1H, m), 6.81 (1H, d), 6.88 (1H, d), 6.94 (1H, m), 6.99 (1H, m), 7.04 (1H, s), 7.24 (1H, m), 7.37 (1H, s), 7.96 (1H, s). Espectro de masa: 531.23 $(MH)^+$.

Ejemplo 27

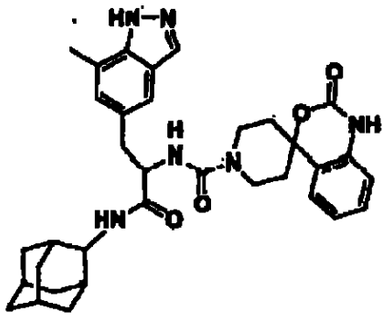
(±)-[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida



^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.68-1.88 (4H, m), 2.47 (3H, m), 2.79 (6H, s), 2.89-3.04 (4H, m), 3.96 (2H, d), 4.75 (1H, m), 6.81 (1H, d), 6.88 (1H, m), 6.93 (1H, m), 6.98 (1H, m), 7.05 (1H, s), 7.24 (1H, m), 7.43 (1H, s), 7.97 (1H, m), 8.32 (1H, s). Espectro de masa: 491.14 $(MH)^+$.

Ejemplo 28

(±)-[1-(2-adamantil-carbamoil)-2-(7-metil-1H-indazol-5-il)-etil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin]-1-carboxamida



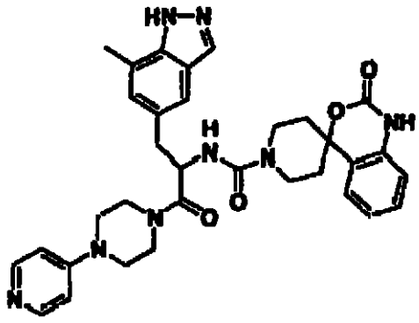
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^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.40-1.95 (15H, m), 2.46 (3H, m), 2.89-3.07 (4H, m), 3.81 (1H, m), 3.90 (2H, m), 4.48 (1H, m), 6.74 (2H, m), 6.86 (1H, d), 6.97 (1H, m), 7.11 (1H, s), 7.24 (1H, m), 7.36 (1H, s), 7.44 (1H, s), 7.96 (1H, s).

Espectro de masa: 597.27 $(MH)^+$.

Ejemplo 29

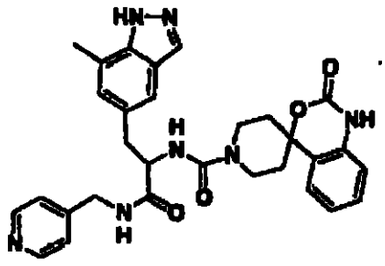
[1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido (±)-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin-1-carboxílico



CL/EM: t_R = 1.56 min, 609.14 $(MH)^+$.

Ejemplo 30

{2-(7-metil-1H-indazol-5-il)-1-[(piridin-4-ilmetil)-carbamoil]-etil}-amida del ácido (±)-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazin-4,4'-piperidin-1-carboxílico

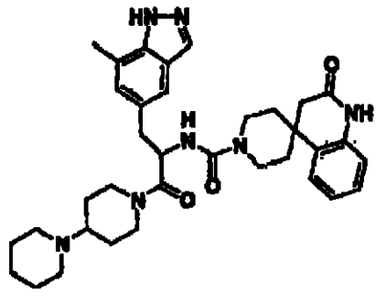


CL/EM: t_R = 1.49 min, 553.12 $(MH)^+$.

947 523

Ejemplo 31

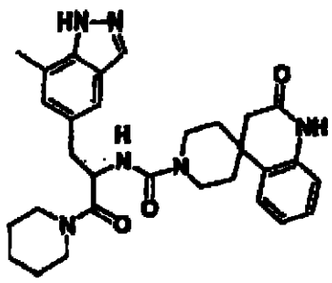
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida



^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.20-2.00 (14H, m), 2.46 (3H, s), 2.38-3.03 (12H, m), 3.87 (2H, m), 4.34 (1H, m), 4.76-4.87 (1H, m), 6.65 (1H, m), 6.82-7.64 (3H, m), 7.13-7.23 (2H, m), 7.36 (3h, m), 7.96 (1H, s). Espectro de masa: 612.32 $(MH)^+$.

Ejemplo 32

(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1-piperidinil]-2-oxoetil]3',4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida

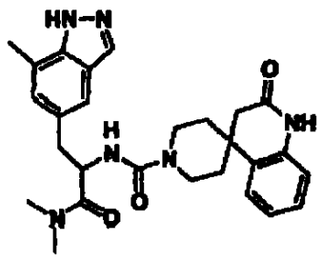


^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.10-1.68 (10H, m), 2.46 (3H, s), 2.50-2.60 (2H, m), 2.82-2.97 (4H, m), 3.39 (2H, m), 3.85

(2H, m), 4.80 (1H, m), 6.68 (1H, m), 6.87 (1H, d), 6.94 (1H, m), 7.03 (1H, s), 7.06 (1H, m), 7.15 (1H, m), 7.37 (1H, s), 7.40 (1H, s), 7.96 (1H, s). Espectro de masa: 529.25 $(MH)^+$.

Ejemplo 33

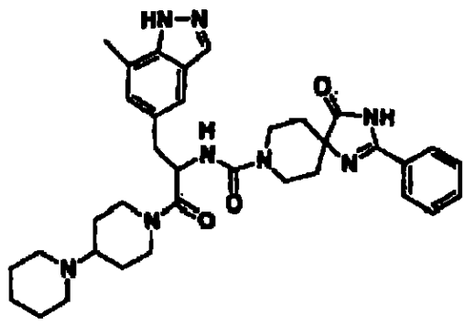
(±)-[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]1,3'4'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinolin]-1-carboxamida



^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.43 (2H, m), 1.56 (2H, m), 2.46 (3H, s), 2.56 (2H, m), 2.79 (3H, s), 2.90 (5H, m), 3.84 (2H, m), 4.73 1H, m), 6.69 (1H, d), 2.69 (1H, d), 6.94 (1H, m), 7.05 (2H, m), 7.14 (1H, m), 7.37 (1H, s), 7.42 (1H, s), 7.96 (1H, s). Espectro de masa: 489.2 $(MH)^+$.

Ejemplo 34

{1-(7-metil-1H-indazol-5-il metil)-2-[1,4]bipiperidinil-1'-il-2-oxo-etil}-amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[4,5]dec-1-ene-8-carboxilico

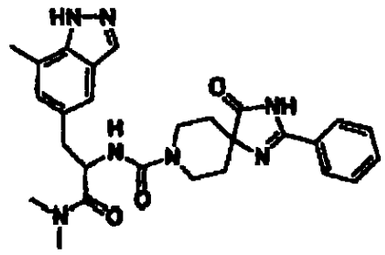


525

^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.34-2.00 (14H, m), 2.48 (3H, s traslapado con DMSO), 2.70-3.30 (12H, m), 3.90 (2H, m), 4.40 m), 4.82 (1H, m), 6.82 (1H, m), 7.04 (1H, s), 7.37 (2H, m), 7.56 (3H, m), 7.98 (3H, m). Espectro de masa: 625.29 $(MH)^+$.

Ejemplo 35

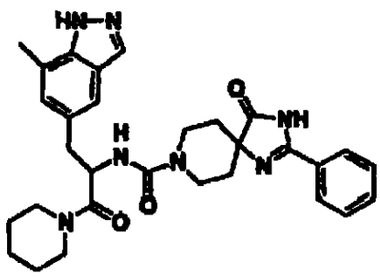
{1-(7-metil-1H-indazol-5-il metil)-2-[1-piperidinilil]-2-oxo-etil}-amida del ácido (±)-4-oxo-2-fenil-1,3,8-triaza-espiro[4,5]dec-1-ene-8-carboxílico



^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.10-1.62 (6H, m), 1.73 (4H, m), 2.48 (3H, s), 3.00 (6H, m), 3.39 (2H, m), 3.93 (2H, m), 4.82 (1H, m), 6.78 (1H, m), 7.05 (1H, s), 7.37 (2H, s), 7.40 (1H, s), 7.53 (2H, m), 7.98 (2H, m). Espectro de masa: 543.26 $(MH)^+$.

Ejemplo 36

[1-dimetilcarbamoil-2-(7-metil-1H-indazol-5-il)-etil]amida del ácido (±)-4-oxo-2-fenil-1,3,8,triaza-espiro[4,5]dec-1-eno-8-carboxílico

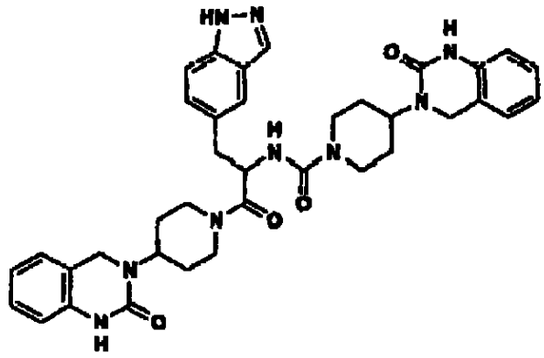


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^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.28-1.61 (4H, m), 2.78 (4H, m), 2.90 (6H, m), 3.94 (2H, m), 4.74 (1H, m), 6.77 (1H, m), 7.05 (1H, s), 7.37 (4H, s), 7.42 (1H, s), 7.52 (2H, m), 7.98 (2H, m). Espectro de masa: 502.21 $(MH)^+$.

Ejemplo 37

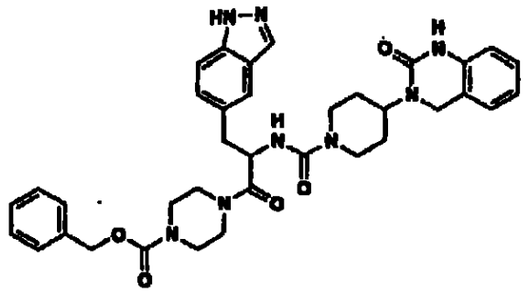
{1-(1H-indazol-5-ilmetil)-2-oxo-2-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-etil}-amida



CL/EM: t_R = 1.674 $(MH)^-$.

Ejemplo 38

Éster de bencilo del ácido 4-(3-(1H-Indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propionil)-piperazin-1-carboxílico

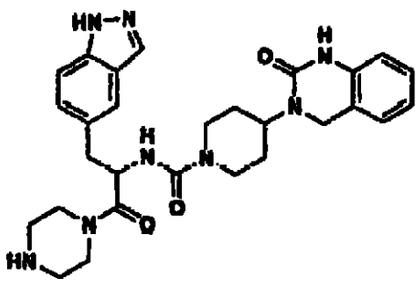


527

CL/EM: t_R = 1.74 min, 665 $(MH)^+$.

Ejemplo 39

[1-(1H-indazol-5-ilmetil)-2-oxo-2-piperazin-1-il-etil]-amida del ácido 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

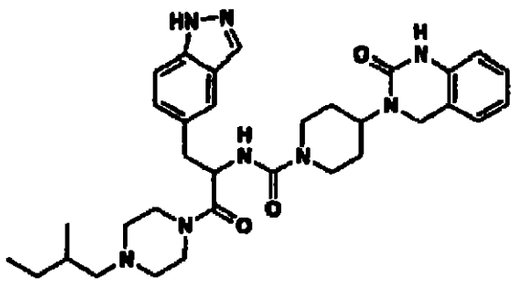


A una solución desgasificada de éster de bencilo del ácido 4-(3-(1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propionil)-piperazin-1-carboxílico (280 mg, 0.42 mmol) en metanol (50 ml) se agregó 10% carbón mineral peletizado (50 mg). La mezcla se agitó en un aparato Parr bajo una atmósfera de hidrógeno a 50 psi (3.515 kg/cm^2) durante 3 h. La mezcla se filtró a través celite. El filtrado se concentró bajo presión reducida para dar el producto deseado en 91% de rendimiento. CL/EM: t_R = 1.22 min, 531 $(MH)^+$.

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Ejemplo 40a

(1-(1H-indazol-5-ilmetil)-2-[4-(2-metil-butil)-piperazin-1-il]-2-oxo-etil)-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

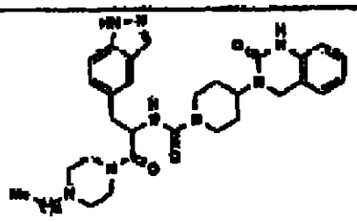
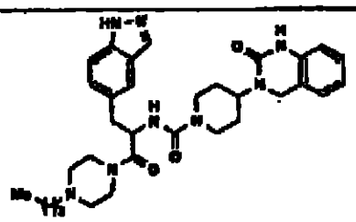
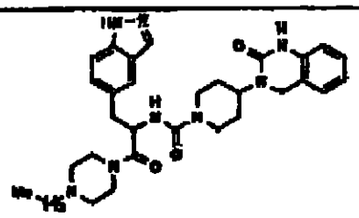
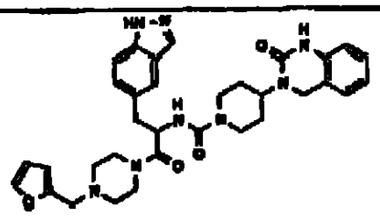


Una solución agitada de [1-(1H-indazol-5-ilmetil)-2-oxo-2-piperazin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (100 mg, 0.188 mmol) en metanol (25 mL) se trató con 2-metil-butiraldehído (0.03 ml, 0.376 mmol). Después de 1 h a temperatura ambiente, se agregó triacetoxiborohidruro de sodio (80 mg, 0.316 mmol). La mezcla se dejo agitar durante la noche. La solución se filtró a través de un cartucho SCX. El cartucho se eluyó primero con metanol y luego con solución 1M de amoniaco en metanol. El solvente se removió in vacuo para dar el producto deseado en 50% de rendimiento. CL/EM: t_R = 1.31 min, 601 $(MH)^+$.

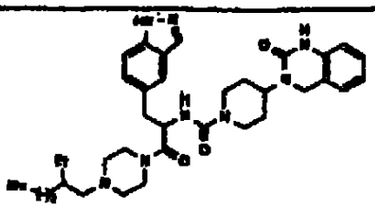
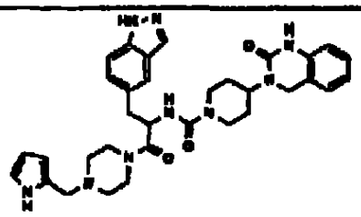
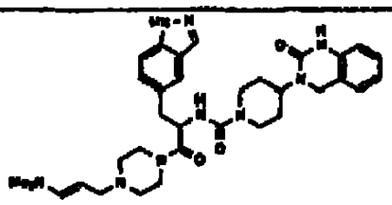
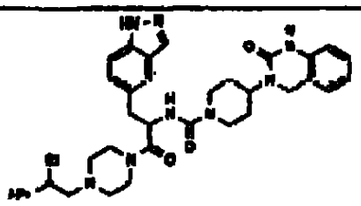
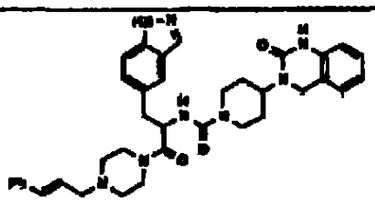
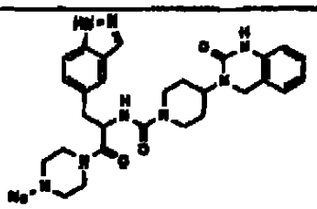
Procedimiento general experimental para la preparación de ejemplos 40b-40k.

Se agregó el aldehído apropiado (0.04 mmol) a una solución del Ejemplo 39 piperazina (0.02 mmol) en metanol (2.0 mL) y la solución resultante se agitó a temperatura ambiente durante 1 h. Luego se agregó el triacetoxiborohidruro de sodio (0.2 mmol) y la solución se dejo agitar durante la noche a temperatura ambiente. La solución luego se filtró a través de un cartucho SCX y el cartucho se lavó con metanol y una solución de amoniaco/metanol. La solución de amoniaco/metanol se concentró in vacuo y los productos crudos se purificaron por CLAR preparativa para proporcionar los productos enlistados en la Tabla 1.

Tabla 1. Ejemplos 40b-40k.

Ejemplo No.	Estructura	CLAR Tiempo de Retención (min)	Espec. de Masa (MH)+
40b		2.62	629
40c		1.41	587
40d		1.27	573
40e		1.74	611

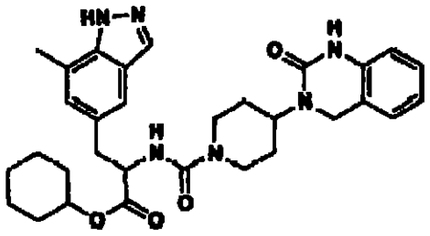
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Ejemplo No.	Estructura	CLAR Tiempo de Retención (min)	Espec. de Masa (MH)+
40f		1.89	643
40g		1.48	610
40h		2.19	614
40i		2.36	629
40j		1.66	647
40k		2.61	545

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Ejemplo 41a

Éster ciclohexilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



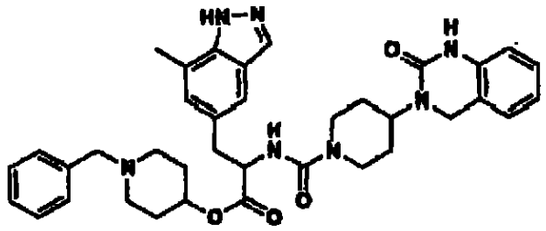
A una solución agitada de ácido (±)-2-amino-3-(7-metil-1H-indazol-5-il)-propiónico (20 mg, 0.042 mmoles), 4-(dimetilamino)piridina (2.5 mg, 0.02 mmoles), y clorohidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (33 mg, 0.17 mmoles) en cloruro de metileno (2 mL) y dimetilformamida (1 mL), se agregó ciclohexanol (13.3 µL, 0.126 mmoles). La mezcla de reacción se agitó a 50-55°C durante 4 h. El solvente se removió bajo presión reducida, el residuo purificado por CCD preparativa en gel de sílice (9:1 cloroformo/metanol) para dar el producto deseado como un sólido blanco (9.4 mg, 40%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.32-1.87 (14H, m), 2.57 (3H, s), 2.86 (2H, m), 3.11-3.26 (2H, m), 4.13-4.22 (3H, m), 4.46 (1H, m), 4.55 (1H, m), 4.80 (1H, m), 6.79 (1H, d), 6.97 (1H, m), 7.08-7.18 (2H, m), 7.35 (1H, s), 7.47 (1H, s), 8.01-8.02 (1H, m). Espectro de masa: 559.22 $(MH)^+$.

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Preparado similarmente:

Ejemplo 41b

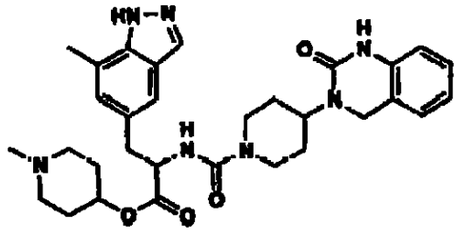
Éster 1-bencil-piperidin-4-ilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: t_R = 1.76 min, 650.30 $(MH)^+$.

Ejemplo 41c

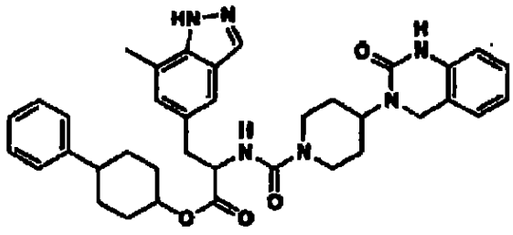
Éster de 1-metil-piperidin-4-ilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: t_R = 1.59 min, 574.27 $(MH)^+$.

Ejemplo 41d

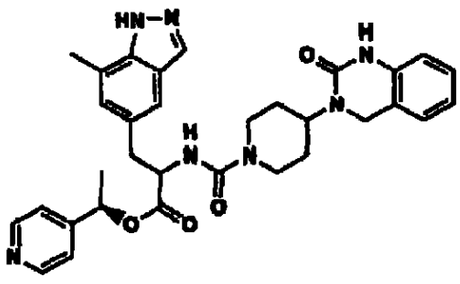
Éster de 4-fenil-ciclohexilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: t_R = 2.69 min, 635.29 $(MH)^+$.

Ejemplo 41e

Éster de (R)-1-piridin-4-il-etilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

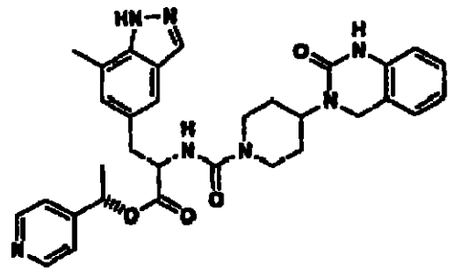


CL/EM: t_R = 1.66 min, 582.22 $(MH)^+$.

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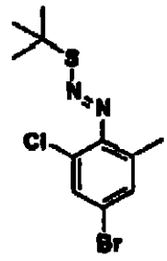
Ejemplo 41 f

Éster de (S)-1-piridin-4-il-etilo del ácido 3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



CL/EM: t_R = 1.65 min, 582.23 $(MH)^+$.

Sulfuro de 4-bromo-2-cloro-6-metilfenildiazo-t-butilo

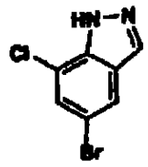


Sulfuro de 4-Bromo-2-cloro-6-metilanilina (4.0 g, 18.3 mmol) se suspendió en 24% ácido clorhídrico (5 mL). La mezcla agitada se enfrió a -20°C y se trató con nitrito de sodio (1.32 g, 1.05 equiv.) en agua (2 mL), gota a gota durante 10 min mientras la temperatura se mantiene debajo de -5°C. Después de unos 30 min adicionales a -5°C hasta -20°C, la

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mezcla se amortiguó a ca. pH 5 con acetato de sodio sólido. Esta mezcla (mantenida a ca. 10°C) se agregó en porciones a una solución agitada de t-butil tiol (2.06 mL, 1 equiv.) en etanol (18.5 mL) a 0°C durante ca. 10 min. Después de la adición, la mezcla se agitó a 0°C durante 30 min y luego se agregó hielo molido (ca. 50 mL). La mezcla se almacenó en el refrigerador durante la noche. El sólido café ligero resultante se recolectó por filtración, se lavó con agua, y se secó bajo alto vacío durante varias horas (4.60 g, 78%). Espectro de masa: 323.03 $(MH)^+$.

5-Bromo-7-cloroindazol

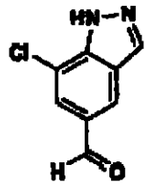


En un matraz de fondo redondo secado a la flama, se combinaron sulfuro de 4-bromo-2,cloro-6-metilfenildiazo-t-butilo (4.60 g, 14.4 mmol) y t-butóxido de potasio (16.1 g, 10 equiv). Una barra de agitación se agregó y la mezcla se colocó bajo nitrógeno. A esto se agregó DMSO seco (50 mL). La mezcla se agitó vigorosamente durante 10 min a temperatura ambiente. La mezcla de reacción luego se vació cuidadosamente en una mezcla de hielo molido (150 mL) y 10% ácido clorhídrico (74 mL). La suspensión resultante se dejó

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que reposara a 4°C durante la noche y el sólido se recolectó por filtración y se lavó con agua. El sólido se recolectó y se secó in vacuo para dar 2.86 g (86%) como un sólido beige. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.52 (d, J = 1.5, 1H), 7.82 (d, J = 1.5, 1H), 8.08 (s, 1H), Espectro de masa: 230.90 $(MH)^+$.

7-cloroindazol-5-carboxaldehído

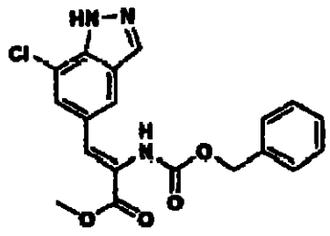


5-bromo-7-cloroindazol (2.0 g, 8.7 mmol) e hidruro de sodio (221 mg, 1.1 equiv) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se agregó tetrahidrofurano seco (30 mL). La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante el cual se volvió homogénea. La mezcla agitada se enfrió a -78°C y una solución de tert-butillitio en pentano (1.7 M, 10.5 mL, 2.0 equiv) se agregó durante varios minutos. Después de 30 min a -78°C, la reacción se permitió estar gradualmente a -50°C, se mantuvo así durante 15 min, y se volvió a enfriar a -78°C. Dimetilformamida (2.8 mL) lentamente se agregó y la mezcla se permitió calendar a -

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50°C. La solución se transfiere rápidamente a un embudo de separación que contienen éter de dietilo y agua. El acuoso se hace ácido por la adición de 1 M sulfato ácido de potasio y se neutraliza por la adición de bicarbonato de sodio. El acuoso se extrajo con éter de dietilo (3x) el cual se lavó con agua, luego salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 1.7 g (100%) de material casi puro. Una muestra pura analíticamente se obtuvo por recristalización de metanol caliente. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.97 (s, 1H), 8.20 (s, 1H), 8.30 (s, (1H), 10.02 (s, (1H). Espectro de masa: 181.09 $(MH)^+$.

Éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-cloro-1H-indazol-5-il)-acrílico

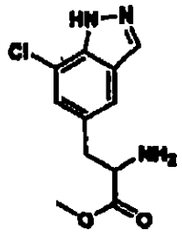


Una suspensión agitada de tert-butóxido de potasio (375 mg, 1.2 equiv.) en cloruro de metileno (20 mL) se enfrió a -20°C y se trata con una solución de éster de trimetilo de N-benciloxicarbonil-α-fosfonoglicina (11 g, 1.2 equiv.) en cloruro de metileno (5 mL). Después de 10 min, se agregó 7-cloroindazol-5-carboxaldehído (0.50 g, 2.79 mmol) en cloruro de metileno (5 mL). La reacción se permitió que se calentara

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gradualmente a temperatura ambiente y se agitó durante 3 dias. La reacción se vació en un embudo de separación que contienen agua y éter de dietilo. El acuoso se extrajo con éter de dietilo (3x) el cual se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró. La cromatografía en columna da 0.40 g (37%) del producto junto con 0.20 g (40%) del material de partida. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 3.64 (s, 3H), 5.11 (s, 2H), 6.44 (bs, 1H), 7.30 (bs, 5H), 7.43 (s, 1H), 7.62 (s, 1H), 7.80 (s, 1H), 8.07 (s, 1H). Espectro de masa: 386.16 $(MH)^+$.

Éster de metilo del ácido (±)-2-Amino-3-(7-cloro-1H-indazol-5-il)-propiónico

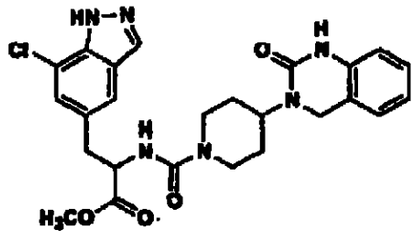


Una solución de éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-cloro-1H-indazol-5-il)-acrílico (300 mg, 0.78 mmol) en metanol (10 mL) se trató con ácido trifluoroacético (0.2 mL), se mojó con nitrógeno, y se trató con 10% paladio en carbón mineral (30 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno. Después de 4 dias, todo el material de partida se

ha consumido. La reacción se mojó con nitrógeno, se filtró a través de celite, y se concentró. La cromatografía en columna da 78 mg (40%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.31 (bs, 3H), 2.95 (dd, J = 13.7, 7.9, 1H), 3.18 (dd, J = 13.7, 5.2, 1H), 3.48 (s, 3H), 3.78 (dd, J = 7.9, 5.2, 1H), 7.23 (s, 1H), 7.46 (s, 1H), 8.00 (s, 1H). Espectro de masa: 254.06 $(MH)^+$.

Ejemplo 42

Éster de metilo del ácido (±)-3-(7-Cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

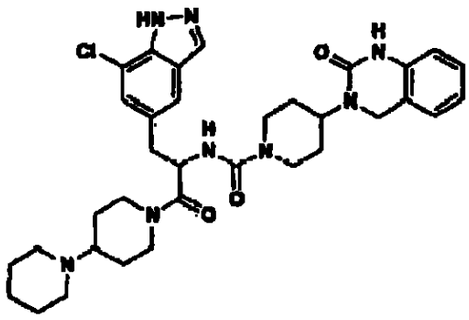


Una solución agitada de éster de metilo del ácido (±)-2-amino-3-(7-cloro-1H-indazol-5-il)-propiónico (78 mg, 0.31 mmol) en tetrahidrofurano (2 mL) a 0°C se trató con carbonil diimidazol (50 mg, 1 equiv). La reacción se agitó durante 5 min, se calentó a temperatura ambiente, y se agitó 10 min, y se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (78 mg, 1.1 equiv). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se purificó por cromatografía en columna para dar 148 mg (94%) como un polvo blanco. ^{1}H-RMN (DMSO-d_6, 500 MHz) δ 1.46 (m, 4H), 2.55-2.80 (m, 2H), 3.05 (dd, J = 13.7, 10.7, 1H), 3.15

(m, 1H), 3.62 (s, 3H), 4.04 (d, J = 13.4, 2H), 4.11 (s, 2H), 4.22-4.39 (m, 2H), 6.76 (d, J = 7.9, 1H), 6.87 (dd, J = 7.3, 7.3, 1H), 6.90 (d, J = 8.2, 1H), 7.08 (d, J = 7.6, 1H), 7.12 (dd, J = 7.6, 7.6, 1H), 7.40 (s, 1H), 7.60 (s, 1H), 8.15 (s, 1H), 9.18 (s, 1H), 13.48 (s, 1H). Espectro de masa: 511.18 $(MH)^+$.

Ejemplo 43

[2-[1,4']bipiperidinil-1'-il-1-(7-cloro-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

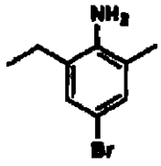


Una suspensión de éster de metilo del ácido (±)-3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (15 mg, 0.029 mmol) en 1:1 tetrahidrofurano/metanol (1 mL) a temperatura ambiente se trató con una solución de hidróxido de litio (3.0 mg, 2.5 equiv) en agua (0.25 mL), y la solución resultante se agitó durante 1.5 h. La solución se enfrió a 0°C, se trató con sulfato de ácido de potasio 1M acuoso (60 µL, 2.0 equiv), y se concentró para dar el ácido crudo el

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cual se usó inmediatamente sin purificación. El ácido crudo se disolvió en (0.3 mL) y se trató secuencialmente con cloruro de metileno (0.15 mL), 4-piperidil-piperidina (10.1 mg, 2 equiv), diisopropiletilamina (10 µL, 2 equiv), y PyBOP® (16.5 mg, 1.1 equiv). La solución se agitó 30 min y se concentró. El producto se purificó por cromatografía en columna para dar 14.7 mg (77%, 2 etapas). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 8H), 1.65-1.88 (m, 5H), 2.14 (m, 1H), 2.23 (m, 1H), 2.30-2.70 (m, 7H), 2.80-3.20 (m, 5H), 3.94 (d, J = 13.4, 13.1, 1H), 4.10-4.30 (m, 4H), 4.55 (m, 1H), 4.62 (dd, J = 13.1, 12.8, 1H), 5.19 (m, 1H), 5.91 (dd, J = 30.2, 22.3, 1H), 6.70 (d, J = 7.6, 1H), 6.92 (dd, J = 7.6, 7.3, 1H), 7.01 (dd, J, 7.9, 7.6, 1H), 7.13 (s, 0.4H), 7.15 (dd, J = 7.9, 7.6, 1H), 7.24 (s, 0.6H), 7.33 (s, 0.4H), 7.43 (s, 0.6H), 7.49 (bs, 1H), 7.91 (s, 0.4H), 7.95 (s, 0.6H), 11.25 bd, J = 50.7, 1H). Espectro de masa: 647.37 $(MH)^+$.

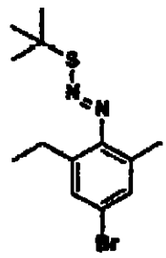
4-bromo-2-etil-6-metil-fenilamina



2-etil-6-metil-fenilamina (14 mL, 100 mmol) se disolvió en ácido clorhídrico concentrado (30 mL) y agua (220 mL) y se enfrió a 0°C. A esto se agregó bromuro (5.1 mL, 1 equiv.)

gota a gota. Esta formación rápida de un precipitado blanco. El precipitado se filtró y se lavó con éter de dietilo. El precipitado se suspendió en agua y se neutraliza con carbonato de potasio acuoso. Un aceite formado el cual se extrajo en éter de dietilo. El etanol se secó sobre carbonato de potasio, se filtró, y se concentró para dar 7.0 g (33%) como un aceite morado el cual se usa sin purificación. Espectro de masa: 214.01 $(MH)^+$.

Sulfuro de 4-Bromo-2-etil-6-metilfenildiazo-t-butilo

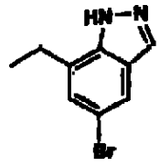


4-bromo-2-etil-6-metilanilina (7.0 g, 33 mmol) se suspendió en 7.8 M de ácido clorhídrico (30 mL). La mezcla agitada se enfrió a -20°C y se trató con nitrato de sodio (2.27 g, 1.05 equiv.) en agua (5 mL), gota a gota durante 10 min mientras la temperatura se mantuvo a debajo de -5°C. Después de unos 30 min adicionales a -5°C hasta 20°C, la mezcla se amortiguó a ca. pH 5 con acetato de sodio sólido. La mezcla se agregó (mantenida a ca. -10°C) en porciones a una solución agitada de t-butil tiol (3.7 mL, 1 equiv.) en etanol (50 mL) a 0°C durante ca. 10 min. Después de la

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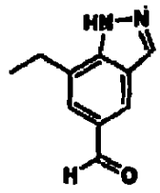
adición, la mezcla se agitó a 0°C durante 30 min y luego se agregó hielo molido (ca. 50 mL). La mezcla se almacenó en el refrigerados durante 2 h. El sólido café ligero resultante se recolectó por filtración, se lavó con agua, y se secó bajo alto vacío durante varias horas (9.47 g, 92%). Espectro de masa: 315.05 $(MH)^+$.

5-bromo-7-etil-1H-indazol



A una solución agitada de t-butóxido de potasio (33.6 g, 10 equiv.) en DMSO (200 mL) se agregó una solución de sulfuro de 4-bromo-2-etil-6-metilfenildiazo-t-butilo (9.4 g, 30 mmol) en DMSO (100 mL) por medio de una cánula. La mezcla se agitó vigorosamente durante 1 h. La mezcla de reacción luego se vació cuidadosamente en una mezcla de hielo molido (500 mL), ácido clorhídrico concentrado (25 mL), y agua (100 mL). El precipitado resultante se filtró, se lavó con agua, se disolvió en metanol, y se concentró para dar 5.7 g (85%) como un sólido marrón. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.39 (t, J = 7.6, 3H), 2.92 (q, J = 7.6, 2H), 7.30 (s, 1H), 7.75 (s, 1H), 8.04 (s, 1H). Espectro de masa: 225.00 $(MH)^+$.

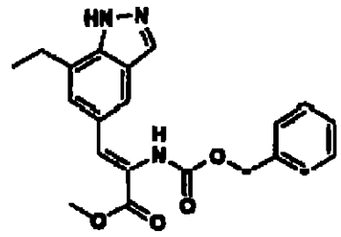
7-Etil-1H-indazol-5-carbaldehído



5-bromo-7-etil-1H-indazol (2.0 g, 8.9 mmol) e hidruro de sodio (226 mg, 1.1 equiv.) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra de agitación magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se agregó tetrahidrofurano seco (60 mL). La mezcla se agitó a temperatura ambiente durante 15 min. La mezcla agitada se enfrió a -78°C y una solución de tert-butillitio en pentano (1.7 M, 10.5 mL, 2.0 equiv.) se agregó durante varios minutos. Después de 15 min a -78°C, la reacción se calentó gradualmente a -50°C, y se volvió a enfriar a -78°C. Dimetilformamida (2.8 mL) se agregó lentamente y la mezcla se permitió calentar a -50°C. La solución se transfiere rápidamente a una solución agitada de agua 300 mL y 1M sulfato ácido de potasio (25 mL). La suspensión resultante se extrajo con éter de dietilo, se lavó con agua, luego salmuera, se secó sobre sulfato de magnesio, y se concentró. La cromatografía en columna da 160 mg (10%) como un sólido blanco. ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.38 (t, J = 7.6, 3H), 2.98 (q, J = 7.6, 2H), 7.71 (s, 1H), 8.22 (s, 1H), 8.24 (s, 1H), 9.96 (s, 1H). Espectro de masa: 175.08 $(MH)^+$.

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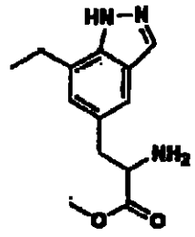
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-etil-1H-indazol-5-il)-acrílico



A una solución agitada de éster de trimetilo de N-benciloxicarbonil-α-fosfonoglicina (0.61 g, 2.0 equiv.) y 7-etil-1H-indazol-5-carbaldehído (160 mg, 0.92 mmol) en tetrahidrofurano (5 mL) a 0°C se agregó tetrametilguanidina (0.22 mL, 1.9 equiv.). La reacción se permitió calentarse lentamente a temperatura ambiente durante la noche. La reacción se concentró, se disolvió en éter de dietilo, se lavó con agua, luego salmuera, se secó (sulfato de magnesio), y se concentró. El residuo se purificó por cromatografía en columna para dar 333 mg (95%) como un aceite. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.33 (t, J = 7.6, 3H), 2.86 (q, J = 7.3, 2H), 3.83 (s, 3H), 5.11 (s, 2H), 6.39 (bs, 1H), 7.29 (bs, 5H), 7.43 (s, 1H), 7.50 (s, 1H), 7.78 (s, 1H), 8.04 (s, 1H). Espectro de masa: 380.17 $(MH)^+$.

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Éster de metilo del ácido (±)-2-Amino-3-(7-etil-1H-indazol-5-il)-propiónico

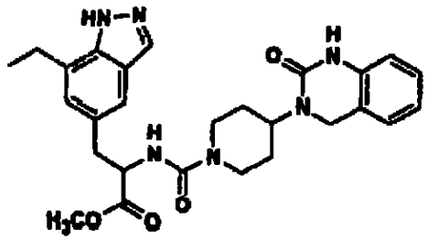


A una solución de éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-etil-1H-indazol-5-il)-acrílico (330 mg, 0.78 mmol) en metanol (5 mL) bajo nitrógeno se agregó paladio en carbón mineral (10%, 33 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró para dar 210 mg (98%) la cual se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.34 (t, J = 7.6, 3H), 2.85 (q, J = 7.6, 2H), 2.96 (dd, J = 13.7, 7.6, 1H), 3.19 (dd, J = 13.7, 8.6, 1H), 3.48 (s, 2H), 3.73 (s, 3H), 3.80 (dd, J = 7.6, 5.2, 1H), 6.99 (s, 7.38 (s, 1H), 7.97 (s, 1H). Espectro de masa: 248.15 $(MH)^+$.

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Ejemplo 44

Éster de metilo del ácido (±)-3-(7-etil-1H-indazol-5-il)-2-{[-4(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

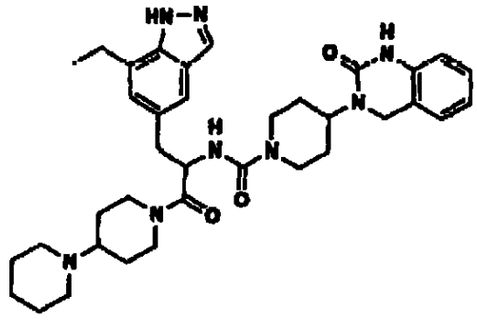


Una solución agitada de éster de metilo del ácido (±)-2-amino-3-(7-etil-1H-indazol-5-il)-propiónico (100 mg, 0.41 mmol) en tetrahidrofurano (2 mL) a 0°C se trató con carbonil diimidazol (66 mg, 1 equiv). La reacción se agitó durante 5 min, se calentó a temperatura ambiente, se agitó durante 15 min, y luego se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (103 mg, 1.1 equiv). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se purificó por cromatografía en columna para dar 188 mg (92%) como un sólido blanco. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.36 (t, J = 7.6, 3H), 1.69 (m, 4H), 2.86 (m, 2H), 2.90 (q, J = 7.6, 2H), 3.22 (dd, J = 5.5, 4.9, 2H), 3.75 (s, 3H), 4.03 (dd, J = 44.0, 13.7, 2H), 4.26 (s, 2H), 4.51 (m, 1H), 4.84 (m, 1H), 5.02 (m, 1H), 6.70 (d, J = 7.9, 1H), 6.90-7.05 (m, 4H), 7.16 (dd, J = 7.6, 7.6, 1H), 7.34 (s, 1H), 8.03 (s, 1H). Espectro de masa: 505.29 $(MH)^+$.

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Ejemplo 45

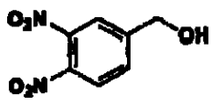
[2-[1,4']bipiperidinil-1'-il-1-(7-etil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster de metilo del ácido (±)-3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (15 mg, 0.03 mmol) en metanol (0.6 mL) se agregó una solución de monohidrato hidróxido de litio (3.0 mg, 2.5 equiv) en agua (0.1 mL), y la solución resultante se agitó durante 6 h. La solución se enfrió a 0°C, se trató con 1M sulfato ácido de potasio acuoso (60 µL, 2.0 equiv), y se concentró para dar el ácido crudo el cual se usó inmediatamente sin purificación. El ácido crudo se disolvió en dimetilformamida (0.4 mL), se enfrió a 0°C, y se trató secuencialmente con cloruro de metileno (0.2 mL), 4-piperidil-piperidina (11 mg, 2.2 equiv), diisopropiletilamina (12 µL, 2.3 equiv.), y PyBOP® (19 mg, 1.2 equiv). La solución se agitó durante 15 min a 0°C, se calentó a temperatura ambiente, se agitó 1.5 h, y se concentró. El producto se purificó por cromatografía en

columna para dar 14.5 mg (76%, 2 etapas). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.28-1.48 (m, 10H), 1.52 (m, 2H), 1.60-1.82 (m, 6H), 1.95 (m, 1.4H), 2.06 (m, 1.6H), 2.20-2.50 (m 5H), 2.77-2.93 (m, 5H), 2.96-3.17 (m, 2H), 3.76 (d, J = 13.4, 0.4H), 3.86 (d, J = 13.7, 0.6H), 4.10-4.20 (m, 2H), 4.26 (s, 2H), 4.57 (m, 2H), 5.10-5.24 (m, 1H), 5.67 (d, J = 8.2, 0.6H), 5.74 (d, J = 7.9, 0.4H), 6.67 (d, J = 7.9, 1H), 5.67 (d, J = 8.2, 0.6H), 5.74 (d, J = 7.9, 0.4H), 6.67 (d, J = 7.9, 1H), 6.93 (dd, J = 7.6, 7.3, 1H), 6.96 (s, 0.4H), 7.03 (dd, J = 7.0, 6.7, 1H), 7.09 (m, 1.6H), 7.15 (d, J = 7.0, 6.7, 1H), 7.31 (s, 0.4H), 7.38 (s, 0.6H), 7.94 (s, 0.4H), 7.95 (s, 0.6H). Espectro de masa: 641.50 $(MH)^+$.

(3,4-Dinitro-fenil)-metanol

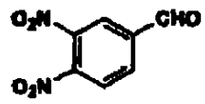


El complejo de borano-tetrahidrofurano (1M en tetrahidrofurano, 800 mL, 800 mmol) se agregó a -20°C durante 45 min a una solución de ácido 3,4-dinitrobenzoico (93.5 g, 441 mmol) en tetrahidrofurano (300 mL). La mezcla resultante se agitó a -20°C durante 1 h y luego se calentó a temperatura ambiente y se agitó durante la noche. Esto se apagó por la adición de 32 mL de 1:1 ácido acético/agua. Los solventes se removieron in vacuo y el residuo se vació en enfriamiento con hielo 1000 mL de bicarbonato de sodio saturado con agitación

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vigorosa durante 15 min. La mezcla se extrajo con acetato de etilo (3 x 500 mL). Las capas orgánicas combinadas se lavaron bicarbonato de sodio saturado, salmuera y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido amarillo ligero (100%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.91 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.71 (dd, J = 8.5, 1.0 Hz, 1H), 4.87 (s, 2H), 2.30 (s, 1H).

3,4-dinitro-benzaldehído

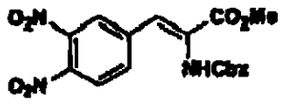


Una solución de (3,4-dinitro-fenil)-metanol (95.3g, 481 mmol) en cloruro de metileno (500 mL) todo se agregó una vez a una suspensión de clorocromato de piridinio (156 g, 722 mmol) en cloruro de metileno (900 mL). La mezcla se agitó a temperatura ambiente durante 1.5 h y luego se agregó éter (1500 mL). El sobrenadante se decantó de la goma blanca resultante, y el residuo insoluble se lavó completamente con cloruro de metileno (3 x 250 mL). La solución orgánica combinada se filtraron a través de una almohadilla de florisilo para proporcionar una solución clara amarilla brillante ligera. Los solventes se removieron in vacuo y el residuo se purificó por cromatografía en gel de sílice usando cloruro de metileno como eluyente para proporcionar el

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compuesto del título como un sólido amarillo. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.45 (d, J = 1.5 Hz, 1H), 8.28 (dd, J = 8.1, 1H), 8.07 (d, J = 8.1 Hz, 1H). ^{13}CRMN (CD_3OD, 125 MHz) δ 187.7, 139.2, 134.2, 126.2, 125.7.

Éster de metilo del ácido 2-benciloxicarbonilamino-3-(3,4-dnitro-fenil)-acrílico



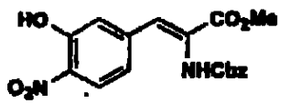
1,1,3,3-Tetrametilguanidina (41.2 mL, 329 mmol) se agregó a temperatura ambiente a una solución de éster de trimetilo de N-(benciloxicarbonil)-alfa-fosfonoglicina (114.1 g, 344 mmol) en tetrahidrofurano (800 mL). La mezcla se agitó a temperatura ambiente durante 15 min y se enfrió a -78°C. Se agregó lentamente una solución de 3,4-dinitro-benzaldehído (61.4 g, 313 mmol) en tetrahidrofurano (200 mL) por medio de una cánula. La mezcla resultante se agitó a -78°C durante 2h y luego se permitió calentar a temperatura ambiente durante la noche. Los solventes se removieron in vacuo, y el residuo amarillo se disolvió en 4.5 L de acetato de etilo. La solución se lavó con 1.5 L de 1N ácido sulfúrico, agua 2 veces, salmuera y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron in vacuo y el residuo se cristalizó de acetato de etilo (20 g producto crudo/100 mL de acetato de etilo). Los cristales amarillos se

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recolectaron y se purificaron además por cromatografía en gel de sílice usando cloruro de metileno como eluyente. El compuesto del título se obtuvo como cristales amarillos (77%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.85 (d, J = 1.5 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.62 (dd, J = 8.5, 1.5 Hz, 1H), 7.35-7.34 (m, 3H), 7.34 (br s, 2H), 7.23 (s, 1H), 6.95 (br s, 1H), 5.07 (s, 2H), 3.90 (s, 3H).

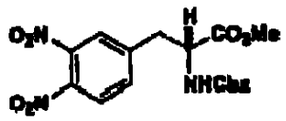
Preparado similarmente:

Éster de metilo del ácido 2-benciloxicarbonilamino-3-(3-hidroxi-4-nitro-fenil)-acrílico



^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.93 (d, J = 9.0 Hz, 1H), 7.32 (br s, sH), 7.28 (br s, 2H), 7.17 (s, 1H), 7.16 (d,J = 2.0 Hz, 1H), 7.01 (dd, J = 9.0, 2.0 Hz, 1H), 6.74 (br s, 1H), 5.06 (s, 2H), 3.86 (s, 3H).

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-dinitro-fenil)-propiónico



Un secado al horno en un matraz Shlenck 500 mL se puso en una bolsa de guante llena con nitrógeno. Después la bolsa

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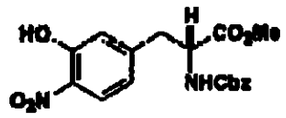
de guante se evacuó y se llenó con nitrógeno (3x), el matraz se selló y se tomó de la bolsa de guante y se pesó. Esto se regresó a la bolsa de guante y se evacuó y se llenó con nitrógeno (3x), luego esto se cargó con trifluorometansulfonato de (-)-1, 2-bis((2R,5R)-2,5-dietilfosfolano)benceno(ciclooctadieneno) rodio (I). El matraz se selló y se tomó de la bolsa de guante y se pesó (784 mg, 1.08 mmol). Éster de metilo del ácido 2-benciloxicarbonilamino-3-(3,4-dinitro-fenil)-acrílico (8.72 g, 21.7 mmol) se agregó a otro matraz Schlenck de 500 mL y se evacuó y se llenó con nitrógeno (3x). Se agregó cloruro de metileno (350 mL, se desgasificó con nitrógeno durante 2 h) y la solución resultante se transfirió al matraz catalizador or medio de una cánula. El matraz se purgó y se llenó con hidrógeno (4x) y la mezcla se agitó a temperatura ambiente durante 4h. Los solventes se removieron in vacuo y el residuo se purificó por cromatografía en gel de sílice usando acetato de etilo/hexanos (1:1) como eluyente para proporcionar el compuesto del título como un sólido gomoso marrón ligero (99% de rendimiento y 99.2% ee determinado por análisis CLAR usando las siguientes condiciones: columna Chiralpak AD (4.6 x 250 mm, 10 um; A = etanol, B = hexano; 40% B @ 1.0 mL/min durante 14 min; tiempo de retención: 10.9 min para el enantiómero R y 6.9 min para el enantiómero S). ^{1}H-RMN ($CDCl_3$,500 MHz) δ 7.80 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H),

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7.45 (d, J = 8.0 Hz, 1H), 7.38-7.31 (m, 5H), 5.37 (d, J = 6.0 Hz, 1H), 5.13-5.05 (m, 2H), 4.68 (d, J = 6.0 Hz, 1H), 3.71 (s, 3H9, 3.36 (dd, J = 13.5, 5.0 Hz, 1H), 3.17 (dd, J = 13.5, 5,6 Hz, 1H).

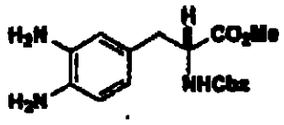
Preparado similarmente:

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3-hidroxi-4-nitro-fenil)-propiónico



^{1}H-RMN ($CDCl_3$, MHz) δ 7.97 (d, J = 9.0 Hz, 1H), 7.36-7.30 (m, 5H), 6.90 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 5.29 (d, j = 7.0 Hz, 1H), 5.11 (d, J = 12.5 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 4.68 (dd, j = 13.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.20 (dd, j = 13.5, 5.0 Hz, 1H), 3.05 (dd, J = 13.5, 6.0 Hz, 1H).

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico

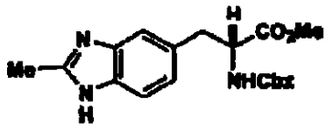


Se agregó formiato de amonio sólido (2.27 g, 36 mmol) en pequeñas porciones a 0°C a una suspensión de metanol (50 mL, desgasificado con nitrógeno durante 2 h) de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-dinitro-fenil)-propiónico (1.45 g, 3.6 mmol) y polvo de zinc (1.41 g, 21.6

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mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche. Los solventes se removieron in vacuo y luego se agregaron tolueno (30 mL, desgasificado) y acetato de etilo (30 mL, desgasificado), seguido por ácido acético (3 mL). La mezcla se diluyó además hasta que se disolvieron todos los sólidos orgánicos, luego esto se lavó con agua, salmuera y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron in vacuo para proporcionar el compuesto del título que contiene 1 equivalente de ácido acético como un sólido gomosa rojizo (85%). Espectro de masa: 344.18 $(MH)^+$.

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-metil-1H-benzoimidazol-5-il)-propiónico

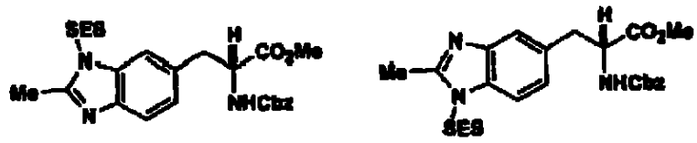


Una solución de ácido acético de éster metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico (640 mg) en ácido acético (8 mL) se calentaron a 130°C durante 4h. La mezcla luego se vació en agua y se enfrió a 0°C. El pH se ajustó a 8 por adición gradual de bicarbonato de sodio sólido. La mezcla luego se extrajo con acetato de etilo (3 x 100 mL), y las capas orgánicas combinadas se lavaron con agua, salmuera y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para

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proporcionar el compuesto del título como un sólido espumoso café (95%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.39 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.26-7.22 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 5.03 (d, J = 12.5 Hz, 1H), 4.99 (d, J = 13.0 hz, 1H), 4.51 (dd, J = 8.5, 5.5 Hz, 1H), 3.70 (s, 3H), 3.27 (dd, J = 13.5, 5.0 Hz, 1H), 3.03 (dd, J = 14.0, 9.0 Hz, 1H), 2.55 (s, 3H). Espectro de masa: 368.19 $(MH)^+$.

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[2-metilo-3-(2-trimetilsilanil-etansulfonil)-3H-benzoimidazol-5-il]-propiónico y éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-1-(2-trimetilsilanil-etansulfonil)-1H-benzoimidazol-5-il]-propiónico

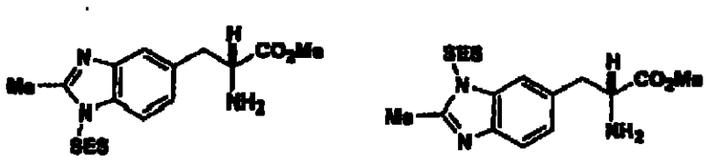


A una suspensión de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-metil-1H-benzoimidazol-5-il)-propiónico (533 mg, 1.96 mmol), y carbonato de sodio en acetonitrilo (20 mL) se agregó cloruro de 2-trimetilsilanil-etansulfonilo puro todo de una vez. La mezcla se agitó a temperatura ambiente durante la noche. Los solventes se removieron y el residuo se purificó por cromatografía en gel de

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sílice usando acetato de etilo/hexanos (1:2) como eluyente para proporcionar el compuesto del título como un sólido ceroso (mezcla 1:1 de isómeros N1 y N368%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 7.68 (d, J = 8.5 hz, 0.5H), 7.55 (d, J = 8.5 Hz, 0.5H), 7.53 (s, 0.5H), 7.41 (s, 0.5H), 7.34-7.29 (m, 5H), 7.06-7.04 (m, 1H), 5.22 (d, J = 8.0 Hz, 0.5H), 5.17 (d, J = 7.5 Hz, 0.5H), 5.11-5.07 (m, 2H), 4.72-4.69 (m, 1H), 3.75 (s, 1.5H), 3.72 (s, 1.5H), 3.24-3.17 (m, 2H), 2.79 (s, 3H), 0.92-0.83 (m, 2H), -0.02 (s, 4.5H), -0.05 (s, 4.5H). Espectro de masa: 532.26 $(MH)^+$.

Éster de metilo del ácido (R)-2-amino-3-[2-metil-1-(2-trimetilsilanil-etansulfonil)-1H-benzoimidazol-5-il]-propiónico y
éster de metilo del ácido (R)-2-Amino-3-[2-metil-3-(2-Trimetilsilanil-etansulfonil)-3H-benzoimidazol-5-il]-propiónico



Una suspensió de metanol (50 mL) de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-[2-metil-3-(2-trimetilsilanil-etansulfonil)-3H-

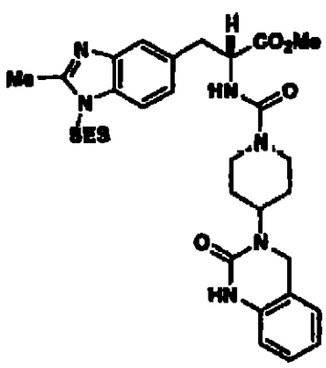
244 559

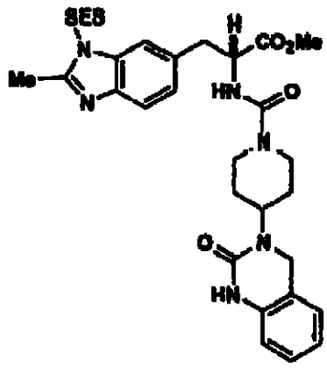
benzoimidazol-5-il]-propiónico y éster metiló del ácido (R)-2-benciloxociarbonilamino-3-[2-metil-1-(2-trimetilsilanil-etansulfonil)-1H-benzoimidazol-5-il]-propiónico (mezcla 1:1, 600 mg), y 10% paladio en carbón mineral (180 mg) se agitaron en un aparato Parr durante la noche bajo 40 psi (2.812 kg/cm^2) de hidrógeno a temperatura ambiente. Después de reemplazar la atmósfera de hidrógeno con nitrógeno, la mezcla se filtró a través de una almohadilla de celite. Los solventes se removieron in vacuo para proporcionar el compuesto del título como un sólido marrón (80%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.81 (d, J = 8.5, 0.5 Hz, 0.5 H), 7.70 (s, 0.5 H), 7.58 (d, J = 8.5 Hz, 0.5 H), 7.49 (s, 0.5 H), 7.25 (d, J = 9.0 Hz, 1H), 3.89 (dd, J = 14.0, 6.5 Hz, 1H), 3.75 (s, 1.5H), 3.72 (s, 1.5H), 3.55-3.51 (m, 2H), 3.18 (d, J = 6.0 Hz, 1H), 3.22-3.18 (m, 0.5H), 3.14-3.09 (m, 0.5H), 2.81 (s, 1.5H), 2.80 (s, 1.5H), 0.92-0.88 (m, 2H), 0.02 (s, 4.5H), 0.01 (s, 4.5H); ^{13}CRMN (CD_3OD, 125 MHz) δ 174.3, 174.1, 153.5, 153.3, 141.7, 140.6, 133.9, 133.82, 133.78, 132.7, 126.5, 126.3, 119.7, 119.0, 114.1, 113.4, 55.6, 51.8, 51.7, 51.6, 40.2, 39.8, 15.83, 15.77, 9.9, -3.07, 3.11. Espectro de masa: 398.20 $(MH)^+$.

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Éster de metilo del ácido (R)-3-[-metil-1-(2-trimetilsilanil-etansulfonil)-1H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico y

Éster de metilo del ácido (R)-3-[2-Metil-3-(2-trimetilsilanil-etansulfonil)-3H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



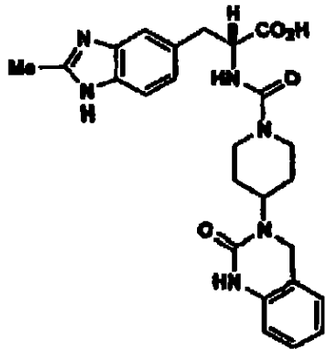


Preparado como se describe arriba para éster de metilo del ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico. Purificado por cromatografía en gel de sílice usando acetato de etilo con 1% trietilamina como eluyente para proporcionar el compuesto del título como un sólido completamente blanco (87%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.82 (d, J = 8.5 Hz, 0.5H), 7.80 (s, 0.5H), 7.59 (d, J = 8.0 Hz, 0.5H), 7.55 (s, 0.5H), 7.33-7.30 (m, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 4.60-4.55

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1H), 4.45-4.40 (m, 1H), 4.29-4.27 (m, 2H), 4.15-4.10 (m, 2H), 3.77 (s, 1.5H), 3.74 (s, 1.5H), 3.56-3.51 (m, 2H), 3.35-3.31 (m, 2H), 3.21-3.15 (m, 1H), 2.91-2.80 (m, 2H), 2.78 (s, 1.5H), 2.77 (s, 1.5H), 1.76-1.73 (m, 1H), 1.66-1.61 (m, 2H), 0.92-0.87 (m, 2H), 0.009 (s, 4.5 H), -0.007 (s, 4.5 H). ^{13}CRMN (CD_3OD, 125 MHz) 173.8, 173.7, 158.2, 158.1, 155.6, 153.4, 153.2, 141.6, 140.3, 137.2, 135.3, 135.1, 133.7, 132.5, 128.2, 126.4, 126.3, 125.7, 122.13, 122.10, 119.6, 118.8, 118.4, 114.0, 113.4, 113.2, 57.3, 56.2, 51.9, 51.7, 51.5, 43.8, 43.7, 42.9, 37.6, 37.2, 28.4, 17.4, 15.7, 15.6, 9.9, -3.1, -3.2. Espectro de masa: 655.36 $(MH)^+$.

Ácido (R)-3-(2-metil-1H-benzoimidazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



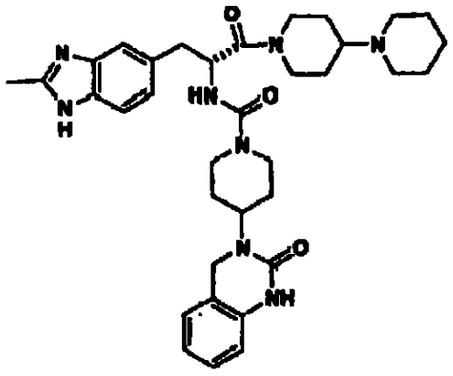
La mezcla 1:1 de éster de metilo del ácido (R)-3-[2-metil-1-(2-trimetilsilanil-etansulfonil)-1H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

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carbonil]-amino}-propiónico y éster de metilo del ácido (R)-3-[2-metil-3-(2-trimetilsilanil-etansulfonil)-3H-benzoimidazol-5-il]-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico se trató como se describe anteriormente para ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-il]-propiónico. Las condiciones de hidrólisis (hidróxido de litio/tetrahidrofurano-metanol-agua (1:1:1) a -15°C durante la noche se usaron. El compuesto del título se obtuvo como un sólido blanco (25%). Espectro de masa: 477.24 $(MH)^+$.

Ejemplo 46

[2-[1,4']bipiperidinil-1'-il-(2-metil-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

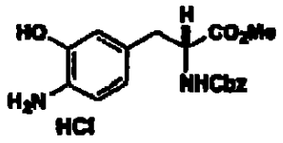


Preparado como se describe arriba para {2-[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida. Purificado

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por cromatografía en gel de sílice usando cloruro de metileno:metanol:trietilamina (93:5:2) como eluyente para dar un sólido blanco. Esto se disolvió en acetato de etilo (60 mL) y se lavó con un 1:1 bicarbonato de sodio/salmuera 2 veces y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido blanco (11% de rendimiento). CL/EM: t_R = 1.59 min, 627.34 $(MH)^+$.

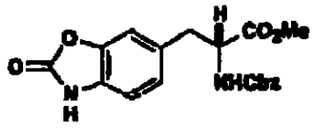
Clorohidrato de éster de metilo del ácido (R)-3-(4-amino-3-hidroxi-fenil)-2-benciloxicarbonilamino-propiónico



Se agregaron hierro en polvo (3.7 g, 66.4 mmol) y cloruro de amonio (5.9 g, 111 mmol) a 0°C a una solución de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3-hidroxi-4-nitro-fenil)-propiónico (2.07 g, 5.53 mmol) en metanol desgasificado 1:1/agua (400 mL). La mezcla resultante se agitó a temperatura ambiente durante 48 h. Se agregó ácido trifluoroacético (7 mL), y la mezcla se revolvió hasta que se obtuvo una solución roja oscura clara que contiene una suspensión de polvo de hierro sin reaccionar. La mezcla se filtró y el filtrado se concentró in vacuo. El residuo se extrajo con acetato de etilo (2 x 150 mL), las capas

orgánicas combinadas se lavaron con salmuera y se secaron sobre sulfato de sodio. Después de la filtración, se agregó ácido clorhídrico (4.2 mL, 4M en dioxano). Los solventes se removieron in vacuo, y el compuesto del título se obtuvo como un sólido espumoso marrón (80%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.34-7.28 (m, 5H), 7.20 (d, J = 8.0 hz, 1H), 6.88 (s, 1H), 6.78 (d, J = 7.5 Hz, 1H), 5.05-5.00 (m, 2H), 4.42 (dd, J = 8.5, 5.0 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 1H), 3.33 (br s, 2H), 3.11 (dd, J = 14.0, 5.0 hz, 1H), 2.90 (dd, J = 13.5, 9.0 Hz, 1H). ^{13}CRMN (CD_3OD, 125 MHz) 172.5, 157.4, 151.2, 140.2, 137.0, 128.5, 128.0, 127.7, 123.8, 120.9, 117.0, 116.9, 67.2, 55.7, 52.0, 37.2. Espectro de masa: 345.20 $(MH)^+$.

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico

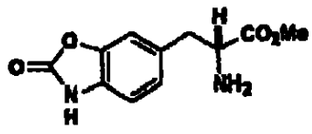


Una solución de cloruro de metileno (15 mL) de carbonil diimidazol (498 mg, 3.07 mmol) se agregó a 0°C a una solución de éster de metilo del ácido (R)-3-(4-amino-3-hidroxi-fenil)-2-benciloxicarbonilamino-propiónico (1.17 g, 3.07 mmol), diisopropiletilamina (1.60 mL, 9.21 mmol), y cloruro de metileno (85 mL). La mezcla se agitó a 0°C durante 4 h. Los solventes se removieron in vacuo y el residuo se purificó por

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cromatografía en gel de sílice usando acetato de etilo/hexanos como eluyente para proporcionar el compuesto del título como un sólido blanco (51%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 9.07 (s, 1H), 7.37-7.29 (m, 5H), 6.96 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.36 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 4.65 (dd, J = 13.5, 5.5 Hz, 1H), 3.74 (s, 3H), 3.17 (dd, J = 14.0, 5.5 Hz, 1H), 3.07 (dd, J = 14.0, 6.0 Hz, 1H). ^{13}CRMN ($CDCl_3$, 125 MHz) δ 171.9, 155.7, 155.5, 144.1, 136.2, 130.8, 128.6, 128.42, 128.38, 128.2, 125.1, 111.1, 109.8, 67.2, 55.1, 52.6, 38.3. Espectro de masa: 371.18 $(MH)^+$.

Éster de metilo del ácido (R)-2-Amino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico

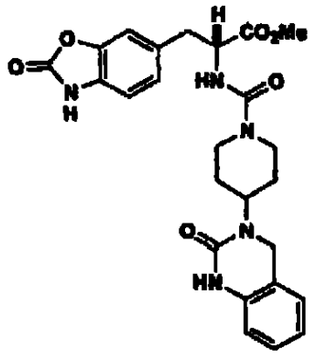


Una solución de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (310 mg) en 4.4% de ácido fórmico en metanol (20 ml, recientemente preparado en metanol desgasificado) se agregó por medio de una cánula a una suspensión de paladio en carbón mineral al 10% en ácido fórmico al 4.4% en metanol (20 ml, recientemente preparado en metanol desgasificado). La mezcla resultante se agitó a temperatura ambiente durante 4

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h. Después de 1 filtración a través de una almohadilla de celite, los solventes se removieron in vacuo dando un sólido marrón. El sólido se disolvió en una mezcla de acetato de etilo (50 mL), tolueno (10 mL) y etanol (40 ml), y se agregó bicarbonato de sodio sólido (3.1 g). La mezcla se agitó a temperatura ambiente durante 2h y se filtró. Los solventes se removieron in vacuo para proporcionar el compuesto del título. ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.41 (br s, 2H), 7.17 (s, 1H), 7.09 (br s, 2H), 4.32 (s, 1H), 3.83 (s, 3H), 3.33 (s, 1H), 3.30 (s, 1H), 3.22 (s, 1H). Espectro de masa: 237.20 $(MH)^+$.

Éster de metilo del ácido (R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-2-[{4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}propiónico

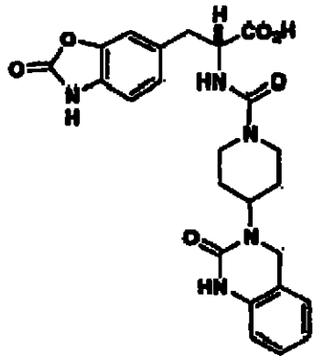


Preparado como se describe arriba para éster de metilo del ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-

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etansulfonil)-1H-indazol-5-il]-propiónico. Purificado por cromatografía en gel de sílice usando cloruro de metileno: metanol:trietilamina (93:5:2) como eluyente para proporcionar el compuesto del título como un sólido blanco (33%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.17-7.13 (m, 3H), 7.08 (d, J = 7.9 hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.55-4.51 (m, 1H), 4.44-4.41 (m, 1H), 4.33 (s, 2H), 4.14-4.10 (m, 2H), 3.74 (s, 3H), 3.33 (br s, 2H), 3.23 (dd, j = 13.7, 5.2 Hz, 1H), 3.03 (dd, J = 14.0, 9.7 Hz, 1H), 2.92-2.82 (m, 2H), 1.79-1.63 (m, 4H). ^{13}CRMN (CD_3OD, 125 MHz) 173.8, 158.2, 156.2, 155.6, 144.4, 137.1, 132.7, 129.3, 128.2, 125.7, 125.0, 122.2, 118.4, 113.4, 110.6, 109.6, 56.2, 52.0, 51.7, 43.8, 42.9, 37.3, 28.4. Espectro de masa: 494.30 $(MH)^+$.

Ácido (R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



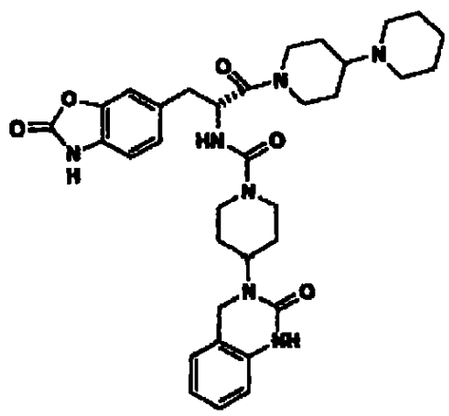
Preparado como se describe arriba para ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil}-amino}-3-[1-(2-trimetilsilanil-etansulfonil)-1H-

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indazol-5-il]-propiónico. Las condiciones de hidrólisis (hidróxido de litio/metanol-tetrahidrofurano-agua (1:1:1) a -15°C durante la noche se usaron. El compuesto del título se obtuvo como un sólido blanco (95%). Espectro de masa: 480.30 $(MH)^+$.

Ejemplo 47

[2-[1,4']bipiperidinil-1'-il-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

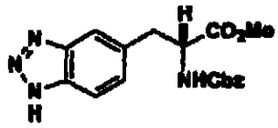


Preparado como se describe arriba para {2-[1,4']-bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. El producto crudo se purificó por cromatografía en gel de sílice usando cloruro de

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metileno:metanol: trietilamina (93:5:2) como eluyente para dar un sólido blanco. Esto se disolvió en acetato de etilo (60 mL) y se lavó con un bicarbonato de sodio saturado 1:1/salmuera 2 veces y se secó sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un sólido blanco (70%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.20-7.14 (m, 4H), 7.08 (d, J = 9.0 Hz, 1H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.99-4.94 (m, 1H), 4.61-4.58 (m, 1H), 4.47-4.43 (m, 1H), 4.39 (s, 1H), 4.23-4.16 (m, 2H), 4.08-4.04 (m, 1H), 3.06-2.88 (m, 5H), 2.74-2.69 (m, 2H), 2.59-2.52 (m, 2H), 2.41-2.33 (m, 2H), 1.96-1.89 (m, 1H), 1.88-1.47 (m, 16H). CL/EM: t_R = 1.86 min, 630.31 $(MH)^+$.

Éster de metilo del ácido (R)-3-(1H-benzotriazol-5-il)-2-benciloxicarbonilamino-propiónico



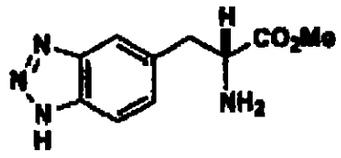
A una solución de mono acetato de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico (2.68 g, 6.65 mmol) en ácido acético

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(30 mL) y agua (40 mL), a temperatura ambiente se agregó una solución de nitrito de sodio (0.46 g, 6.65 mmol) en agua (8 mL), gota a gota durante varios minutos. La mezcla resultante se agitó a temperatura ambiente durante 20 min, luego se enfrió a 0°C, hidróxido de amono concentrado se agregó para ajustar el pH a 11. La mezcla se extrajo con acetato de etilo 2 veces en presencia de cloruro de sodio sólido, y las capas orgánicas se secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron in vacuo y el residuo se purificó por cromatografía en gel de sílice usando acetato de etilo/hexanos (6:4) como eluyente para proporcionar el compuesto del título como un sólido marrón (94% de rendimiento). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.75 (d, J = 8.5 Hz, 1H), 7.58 (s, 1H), 7.31-7.25 (m, 5H), 7.18 (d, J = 8.5 Hz, 1H), 5.39 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.05 (d, J = 12.0 Hz, 1H), 4.74 (dd, j = 13.5, 6.0 Hz, 1H), 3.73 (s, 3H), 3.34 (dd, J = 14.0, 5.5 Hz, 1H), 3.22 (dd, J = 13.5, 6.0 Hz, 1H), ^{13}CRMN (CD_3OD, 125 MHz) δ 172.1, 156.0, 136.1, 128.6, 128.3, 128.1, 67.2, 55.2, 52.7, 38.5. Espectro de masa 355.18 $(MH)^{+}$.

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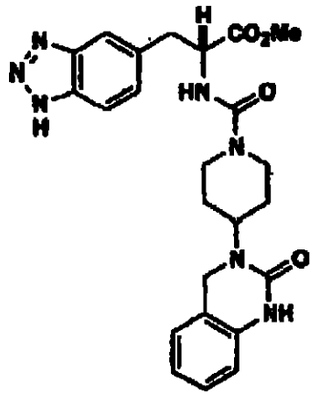
Ester de metilo del ácido (R)-2-amino-3-(1H-benzotriazol-5-il)-propiónico



Preparado como se describió por el éster de metilo del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.38 (br s, 2H), 7.89 (d, J = 7.5 Hz, 1H), 7.81 (s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 4.44 (s, 1H), 3.81 (s, 3H), 3.48-3.45 (m, 1H), 3.40-3.37 (m, 1H), 3.33 (br s, 1H). ^{13}C RMN (CD_3OD, 125 MHz) δ 169.8, 139.4, 138.9, 133.0, 127.6, 115.52, 115.47, 54.3, 52.6, 36.7. Espectro de masa 221.15 $(MH)^+$.

Ejemplo 48

Éster de metilo del ácido (R)-3-(1H-Benzotriazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



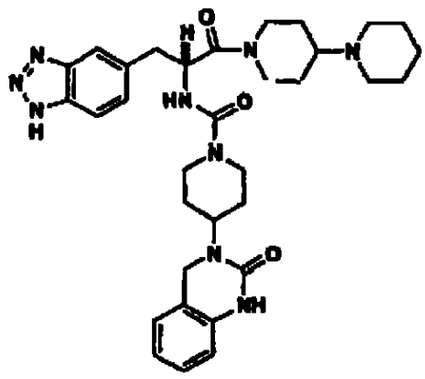
Preparado como se describió por el éster de metilo del

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ácido (R)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-[1-(2-trimetilsilanil-etanosulfonil)-1H-indazol-5-il]-propiónico excepto que el carbonil diimidazol se usó en lugar de carbonato de N,N-disuccinimidilo (DSC). ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.82 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.39 (dd, J = 8.7, 1.2 Hz, 1H), 7.15-7.08 (m, 2H), 6.94 (td, J = 7.5, 0.9 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 4.67-4.60 (m, 1H), 4.39-4.31 (m, 1H), 4.15 (s, 2H), 4.08-4.03 (m, 2H), 3.72 (s, 3H), 3.38 (dd, J = 13.9, 5.5 Hz, 1H), 3.32-3.29 (m, 1H), 3.17 (dd, J = 13.9, 10.3 Hz, 1H), 2.87-2.71 (m, 2H), 1.64-1.48 (m, 4H). Espectro de masa 478.30 $(MH)^+$.

Ejemplo 49

[1-(1H-benzotriazol-5-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

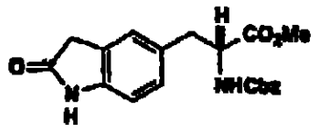


Preparado como se describió por {2-[1,4']bipiperidinil-

549 573

1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil)-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Se purificó por cromatografía en gel de sílice usando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente. ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.83 d, J = 8.2 Hz, 0.75H), 7.79 (d, J = 8.5 Hz, 0.25H), 7.71 (s, 0.25H), 7.69 (s, 0.75H), 7.33 (d, J = 9.2 Hz, 1H), 7.16-7.12 (m, 2H), 6.96-6.91 (m, 1H), 6.78 (d, J = 8.0 Hz, 0.75H), 6.77 (d, J = 8.0 Hz, 0.25H), 5.07-5.03 (m, 1H), 4.58-4.55 (m, 1H), 4.45-4.40 (m, 1H), 4.34 (s, 1.25H), 4.24 (s, 0.75H), 4.20-4.05 (m, 2.25H), 4.00-3.96 (m, 0.75H), 3.24-3.09 (m, 2H), 2.91-2.78 (m, 4H), 2.64-2.61 (m, 2H), 2.56-2.42 (m, 2H), 2.15-2.10 (m, 1.25H), 2.02-1.98 (m, 1.75H), 1.95-1.90 (m, 1H), 1.68-1.60 (m, 8H), 1.54-1.46 (m, 6H). CL/EM: t_R = 1.86 min, 614.28 $(MH)^+$.

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-1H-indazol-5-il)-propiónico



El $PyHBr_3$ (1.28 g, 4.02 mmol) se agregó en pequeñas porciones durante 30 minutos a una solución de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(1H-indol-5-il)-propiónico (0.47 g, 1.34 mmol) en t-butanol (10 mL)

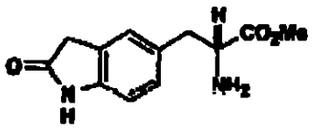
574

mientras la temperatura de reacción se mantuvo entre 25-30°C. La mezcla resultante se agitó a temperatura ambiente durante 3.5 h. El solvente se removió in vacuo, y el residuo se extrajo con acetato de etilo (2x). Las fases orgánicas combinadas se lavaron con salmuera y se secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron y el residuo se secó azeotrópicamente con etanol anhidro. El residuo se disolvió en ácido acético glacial (10 mL) y polvo de zinc (0.88 g, 13.4 mmol) se agregó. La mezcla se agitó a temperatura ambiente durante la noche. Después de que el ácido acético se removió in vacuo, el residuo se purificó por cromatografía instantánea en gel de sílice usando acetato de etilo/hexanos [(1:3) primero y luego (3:2)] como eluyente para proporcionar el compuesto del título como un sólido blanco (41% durante 2 etapas). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 8.03 (s, 1H), 7.36-7.31 (m, 5H), 6.94 (s, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 5.26 (d, J = 8.0 Hz, 1H), 5.11 (d, J = 12.0 Hz, 1H), 5.05 (d, j = 12.5 Hz, 1H), 4.61 (dd, J = 13.5, 6.0 Hz, 1H), 3.72 (s, 3H), 3.45 (s, 2H), 3.10 (dd, J = 14.0, 5.5 Hz, 1H), 3.00 (dd, J = 14.0, 6.0 Hz, 1H). ^{13}C RMN ($CDCl_3$, 125 MHz) δ 177.7, 172.2, 155.7, 141.7, 136.3, 129.8, 128.9, 128.6, 128.3, 128.2, 125.8, 125.6, 109.8, 67.1, 55.1, 52.5, 38.0, 36. Espectro de masa 369.20 $(MH)^+$.

Éster de metilo del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-

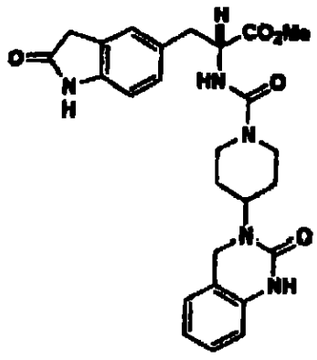
575

1H-indol-5-il)-propiónico



Preparado como se describió por éster de metilo del ácido (R)-2-amino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. ^{1}H-RMN (CD_3OD, 500 MHz) δ 8.48 (br s, 2H), 7.16 (s, 1H), 7.10 (s, 1H), 6.89 (s, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 3.54 (s, 1H), 3.33 (s, 2H), 3.20 (s, 1H), 3.12 (s, 1H). ^{13}C RMN (CD_3OD, 125 MHz) δ 178.9, 170.7, 143.3, 129.0, 128.6, 126.9, 125.6, 110.0, 57.3, 54.6, 52.3, 37.0. Espectro de masa 235.30 $(MH)^+$.

Éster de metilo del ácido (R)-3-(2-oxo-2,3-dihidro-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

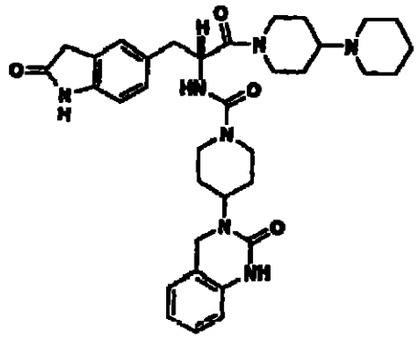


Una solución de fosgeno en tolueno (2M, 0.158 mL, 0.30

mmol) se agregó a una mezcla agitada vigorosamente de éster de metilo del ácido propiónico (70 mg, 0.25 mmol) en cloruro de metileno (15 mL) y bicarbonato de sodio saturado (7.5 mL). Después de que la mezcla se agitó a temperatura ambiente durante 30 minutos, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (58 mg, 0.25 mmol) se agregó. La mezcla resultante se agitó a temperatura ambiente durante 1.5 h, se diluyó con acetato de etilo, y se lavó con 0.25 N ácido clorhídrico que estaba saturado con cloruro de sodio sólido. La capa orgánicas se secaron sobre sulfato de sodio. Después de la filtración, los solventes se removieron para proporcionar el compuesto del título como un aceite viscoso color marrón. CL/EM: t_R = 2.01 min, 492.10 $(MH)^+$.

Ejemplo 50

[2-[1,4']bipiperidinil-1'-il-2-oxo-1-(2-oxo-2,3-dihidro-1H-indol-5-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

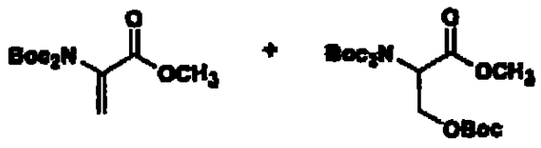


Preparado como se describió por el [2-

J-44 577

[1,4']bipiperidinil-1'-il-2-oxo-1-[1-(2-trimetilsilanil-etansulfonil)-1H-indazol-5-ilmetil]-etil}-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico. Se purificó por cromatografía instantánea en gel de sílice usando cloruro de metileno/metanol/trietilamina (93:5:2) como eluyente. ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.20-7.09 (m, 4H), 6.97 (t, J = 7.3 Hz, 1H), 6.88 (d, J = 7.9 Hz, 0.65 H), 6.84 (d, J = 7.6 Hz, 0.35 H), 6.80 (d, J = 7.7 Hz, 1H), 5.51 (s, 0.65 H), 5.23 (s, 0.35 H), 4.99-4.95 (m, 0.65 H), 4.92-4.88 (m, 0.35 H), 4.60-4.56 (m, 1.65 H), 4.46-4.41 (m, 1.35 H), 4.39 (s, 1.3 H), 4.36 (s, 0.7 H), 4.24-4.17 (m, 2H), 4.05-4.02 (m, 1H), 3.65-3.61 (m, 2H), 3.52-3.47 (m, 1H), 3.20-3.16 (m, 1H), 3.00-2.88 (m, 2H), 2.70-2.64 (m, 2H), 2.53-2.46 (m, 2H), 2.40-2.34 (m, 2H), 1.94-1.46 (m, 15H), 1.39-1.36 (m, 2H). CL/EM: t_R = 1.83 min, 628.40 $(MH)^+$.

Éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-acrílico

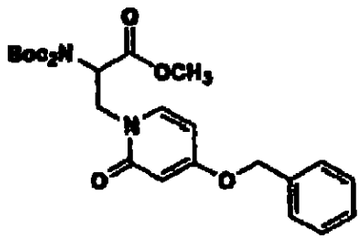


A una solución de éster de metilo del ácido 2-tert-butoxicarbonilamino-3-hidroxi-propiónico (10.0 g, 39 mmol) y di-tert-butil-dicarbonato (21.8 g, 2.6 equiv.) en

JLF 578

acetonitrilo (40 mL) se agregó 4-dimetilaminopiridina (0.48 g, 0.1 equiv) a temperatura ambiente. La solución se agitó durante la noche y se concentró. El residuo se disolvió en éter de dietilo, se lavó secuencialmente con sulfato ácido de potasio 1 M (2x), bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 15.6 g (cuant.) como un aceite. La inspección de RMN mostró una mezcla del compuesto del título y éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-3-tert-butoxicarboniloxi-propiónico. Como esto se encontró al último que ambos se hicieron reaccionar con aminas secundarias para dar los mismos productos, la mezcla se usó sin separación. Éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-acrílico: ^{1}H-RMN ($CDCl_3$) δ 1.45 (s, 18H), 3.78 (s, 3H), 5.63 (s, 1H), 6.33 (s, 1H). Espectro de masa: 324.14 $(M+Na)^+$. Éster de metilo del ácido 2-(Di-tert-butoxicarbonilamino)-3-tert-butoxicarboniloxi-propiónico. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 1.49 (s, 18H), 3.72 (s, 3H), 4.42 (dd, J = 11.6, 9.2, 1H), 4.75 (dd, J = 11.3, 4.6, 1H), 5.30 (dd, J = 9.2, 4.6, 1H). Espectro de masa: 442.21 $(M+Na)^+$.

Éster de metilo del ácido (±)-3-(4-benciloxi-2-oxo-2H-piridin-1-il)-2-(di-tert-butoxicarbonilamino)-propiónico

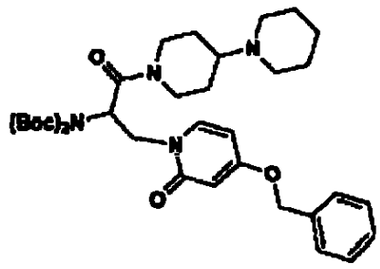


A una solución de éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-acrílico (900 mg, 3.0 mmol), y (630 mg,

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1.03 equiv) en acetonitrilo (2.5 mL) se agregó carbonato de cesio (100 mg, 0.10 equiv). La suspensión resultante se calentó a 80°C en un microondas durante 2 h. La reacción se concentró, se disolvió en agua, y se extrajo con cloruro de metileno (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, y se concentraron para dar 1.47 g (97%) el cual se uso sin purificación adicional. Espectro de masa: 503.56 $(MH)^+$.

(±)-4-benciloxi-1-[3-[1,4']bipiperidinil-1'-il-2-(di-tert-butoxicarbonilamino)-3-oxo-propil]-1H-piridina-ona



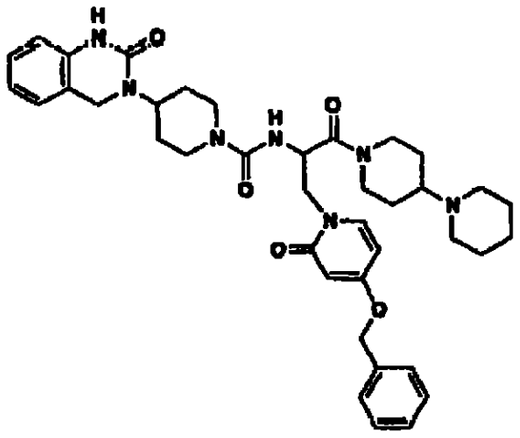
A una solución agitada de éster de metilo del ácido 3-(4-benciloxi-2-oxo-2H-piridin-1-il)-2-(di-tert-butoxicarbonilamino)-propiónico (1.47 g, 2.9 mmol) en metanol (17 mL) se agregó una solución de monohidrato hidróxido de litio (0.50 g, 4 equiv) en agua (2.85 mL). La mezcla de reacción se agitó durante 3 h a temperatura ambiente, se enfrió para tratarse con ácido clorhídrico concentrado (0.99 mL), y se concentró para proporcionar el ácido crudo, la mitad del cual se tomo en la siguiente etapa. El ácido crudo se disolvió en cloruro de metileno (6 mL), se enfrió a 0C y

600 580

se trató secuencialmente con 4-piperidil-piperidina (0.25 g, equiv), trietilamina (0.31 mL, 2.5 equiv), y cloruro de bis-2-oxo-3-oxazolidinil)fosínico (0.38 g, equiv). La reacción se permitió calentar a temperatura ambiente y se agitó durante la noche. La reacción se concentró, y se purificó por CLAR preparativa para proporcionar 489 mg (52%, 2 etapas). Espectro de masa: 639.41 $(MH)^+$.

Ejemplo 51

[1-(4-benciloxi-2-oxo-2H-piridin-1-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2-H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución agitada de 4-benciloxi-1-[3-[1,4']bipiperidinil-1'-il-2-(di-tert-butoxicarbonilamino)-3-oxo-propil]-1H-piridin-2-ona en cloruro de metileno (3 mL) se agregó ácido trifluoroacético (1 mL) a 0°C. Después de 2 h, la

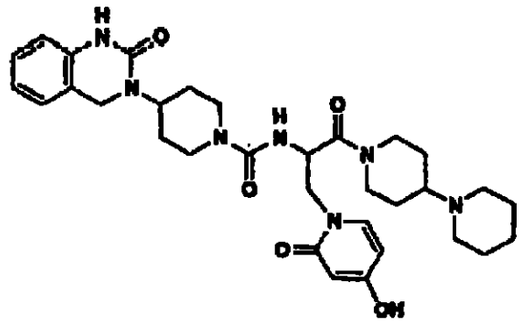
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reacción se concentró para proporcionar la amina cruda (151 mg, 97%) a esta sal del ácido trifluoroacético [Espectro de masa: 439.61 $(MH)^+$] la cual se dividió en dos porciones, usando la mitad en el siguiente procedimiento. A una solución de la amina cruda (75 mg, 0.11 mmol) y diisopropiletilamina (80 µl, 4 equiv.) en cloruro de metileno (3 mL) a 0°C se agregó carbonil diimidazol (29 mg, 1.6 equiv, en 2 porciones). Después de agitar durante 10 min, la solución se trató con ácido 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-acético (40 mg, 1.15 equiv). La reacción se calentó a temperatura ambiente y se agitó durante la noche. La reacción se concentró y se purificó por CDD preparativa para dar 40.8 mg (53%). ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.25-1.56 (m, 4H), 1.56-1.84 (m, 9H), 1.90-2.08 (m, 2H), 2.60-2.95 (m, 8H), 3.11 (dd, J = 24.1, 12.8, 1H), 3.89 (ddd, J = 22.0, 13.2, 9.2, 1H), 4.10 (dd, J = 14.3, 14.1, 2H), 4.27-4.54 (m, 5H), 4.60 (bd, J = 11.9, 1H), 5.08 (dd, J = 13.2, 12.2, 2H), 5.26 (ddd, J = 9.4, 4.8, 1H), 6.05 (dd, J = 13.7, 2.7, 1H), 6.16 (m, 1H), 6.77 (d, J = 8.0, 1H), 6.84 (ddd, J = 7.6, 7.6, 2.1, 1H), 7.04 (d, J = 7.6, 1H), 7.12 (dd, J = 7.6, 7.4, 1H), 7.28-7.43 (m, 5H), 7.48 (d, J = 7.6, 1H). Espectro de masa: 696.85 $(MH)^+$.

582

Ejemplo 52

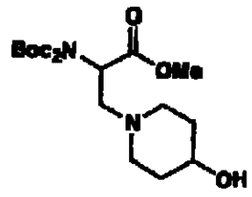
[2-[1,4']bipiperidinil-1'-il-1-(4-hidroxi-2-oxo-2H-piridin-1-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Una solución agitada de [1-(4-benciloxi-2-oxo-2H-piridin-1-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (29 mg) y 10% paladio en carbón mineral (5 mg) en metanol (1 mL) se coloco bajo una atmósfera de hidrógeno. Después de 1 h a temperatura ambiente, la reacción se mojó con nitrógeno, se filtró a través celite, y se concentró para dar el producto. ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.40-1.85 (m, 12H), 2.04 (dd, J = 27.4, 17.0, 2H), 2.66 (dd, J = 21.1, 11.0, 1H), 2.80-3.19 (m, 8H), 3.95 (ddd, J = 49.8, 12.5, 7.9, 1H), 4.07-4.28 (m, 3H), 4.34 (bs, 2H), 4.36-4.59 (m, 2H), 4.63 (bd, J = 12.8, 1H), 5.20 (m, 1H), 5.75 (dd, J = 7.3, 2.1, 1H), 5.97 (dd, J = 8.9, 7.6, 1H), 6.78 (d, J = 7.6, 1H), 6.93 (dd, J = 7.6, 7.3, 1H), 7.08-7.18 (m, 2H), 7.33 (dd, J = 18.3, 11.0, 1H). Espectro de masa: 606.32 $(MH)^+$.

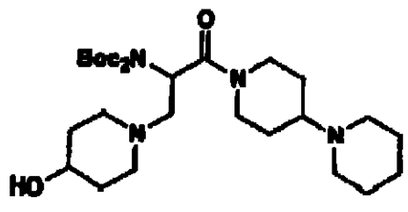
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Éster de metilo del ácido (±)-2-(di-tert-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propiónico



A una solución de éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-acrílico (1.0 g, 3.0 mmol) en acetonitrilo (10 mL) se agregó piperidin-4-ol (0.33 g, 1.1 equiv). Una corriente suave de nitrógeno se colocó durante la reacción mientras esta se agitó durante la noche. El aceite crudo el cual resulto se disolvió en acetato de etilo, se lavó con agua, luego salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 1.38 g (cuant.) como un aceite el cual se uso sin purificación adicional. Espectro de masa: 403.42 $(MH)^+$.

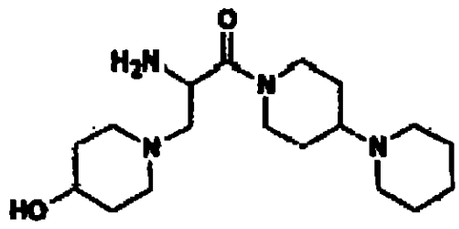
(±)-1-[1,4']bipiperidinil-1'-il-2-(di-tert-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propano-1-ona



604 584

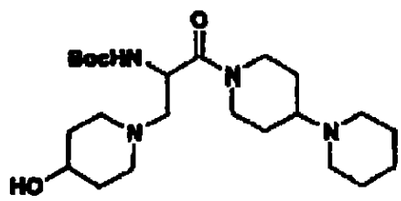
A una solución de éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propiónico (1.0 g, 2.5 mmol) en metanol (6 mL) se agregó una solución de monohidrato hidróxido de litio (400 mg, 3.9 equiv.) en agua mL). La reacción se agitó 6 h, se enfrió hasta neutralizarse con ácido clorhídrico concentrado, y se concentró. El ácido crudo se usó sin purificación. El ácido crudo se suspendió en cloruro de metileno (25 mL), se trató con algunas gotas de metanol para ayudar a disolver el ácido, y se enfrió a 0°C. La suspensión resultante se trató secuencialmente con 4-piperidil-piperidina (0.53 g, 1.25 equiv), trietilamina (0.70 mL, 2. equiv), y cloruro de bis-2-oxo-3-oxazolidinil)fosínico (0.80 g, 1.25 equiv). La reacción se permitió calentar a temperatura ambiente durante la noche. La reacción se concentró y luego se purificó por CLAR preparativa para proporcionar 310 mg (23%, 2 etapas). Espectro de masa: 539.49 $(MH)^+$.

(±)-2-amino-1-[1,4']bipiperidinil-1'-il-3-(4-hidroxi-piperidinil-1-il)-propano-1-ona



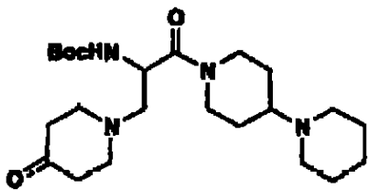
A una solución de 1-[1,4']bipiperidinil-1'-il-2-(di-tert-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propan-1-ona (310 mg, 0.58 mmol) en cloruro de metileno (5 mL) a 0°C, se agregó ácido trifluoroacético (2.0 ml). El baño de hielo se removió y la reacción se agitó durante 30 min. La reacción se concentró para proporcionar el producto como esta sal del ácido trifluoroacético (400 mg, cuant.) la cual se uso sin purificación adicional. Espectro de masa: 339.46 $(MH)^+$.

Éster de tert-butilo del ácido (±)-[2-[1,4']bipiperidinil-1'-il-1-(4-hidroxi-piperidin-1-ilmetil)-2-oxo-etil]-carbámico



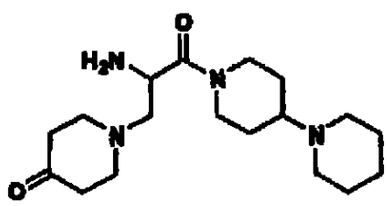
A una solución de 2-amino-1-[1,4']bipiperidinil-1'-il-3-(4-hidroxi-piperidin-1-il)-propan-1-ona (sal del ácido trifluoroacético, 300 mg, 0.58 mmol) y diisopropiletilamina (0.30 mL, 4 equiv) en tetrahidrofurano (5 mL) se agregó di-tert-butil-dicarbonato (128 mg, 1 equiv). La solución resultante se agitó a temperatura ambiente durante 1 h, y se concentró. El residuo se disolvió en acetato de etilo, se lavó con agua, luego salmuera, se secó sobre sulfato de magnesio, y se concentró para proporcionar hasta 248 mg (98%) el cual se uso sin purificación adicional. Espectro de masa: 439.65 $(MH)^+$.

Éster de tert-butilo del ácido (±)-[2-[1,4']bipiperidinil-1'-il-2-oxo-1-(4-oxo-piperidin-1-ilmetil)-etil]-carbámico



A una solución de 1-[1,4']bipiperidinil-1'-il-2-(di-tert-butoxicarbonilamino)-3-(4-hidroxi-piperidin-1-il)-propan-1-ona (200 mg, 0.37 mmol) en cloruro de metileno (4 mL) se agregó peryodinano Dess-Martin (316 mg, 2 equiv) en dos porciones. Después de 1 h, la reacción se apagó por la adición de bicarbonato de sodio saturado, y se extrajo en cloruro de metileno (3x). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, y se concentraron para dar 187 mg (94%) el cual se uso sin purificación adicional. Espectro de masa: 437.63 $(MH)^+$.

(±)-1-(2-amino-3-[1,4']bipiperidinil-1'-il-3-oxo-propil)-piperidin-4-ona



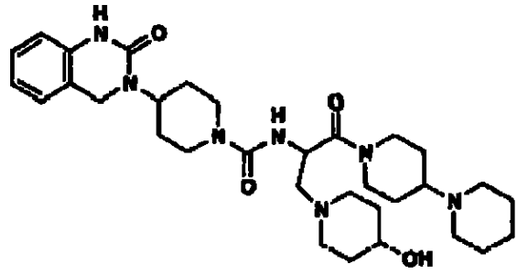
A una solución de éster de tert-butilo del ácido [2-[1,4']bipiperidinil-1'-il-2-oxo-1-(4-oxo-piperidin-1-

587

illmetil)-etil]-carbámico (100 mg, 0.23 mmol) en cloruro de metileno (5 mL) a 0°C, se agregó ácido trifluoroacético. El baño de hielo se removió, se agitó continuamente durante 1 h, y la reacción se concentró para dar 150 mg (96%) como esta sal del ácido trifluoroacético, la cual se uso sin purificación adicional. Espectro de masa: 337.64 $(MH)^+$.

Ejemplo 53

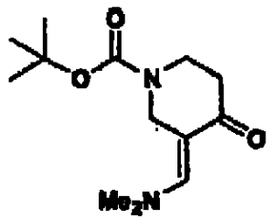
[2-[1,4']bipiperidinil-1'-il-1-(4-hidroxi-piperidin-1-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de [2-[1,4']bipiperidinil-1'-il-1-(4-hidroxi-piperidin-1-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (sal del 3 ácido trifluoroacético, 200 mg, 0.39 mmol) en cloruro de metileno (5 mL) a 0°C, se agregó diisopropiletilamina (0.27 mL, 3.9 equiv), y carbonil diimidazol (63 mg, equiv). Después de agitar durante 15 min, la solución se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (sal del ácido acético, 142 mg, 1.25 equiv).

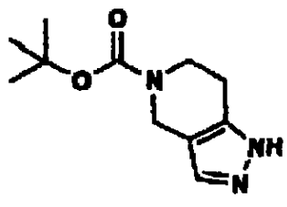
La solución se calentó a temperatura ambiente y se agitó durante la noche. La reacción se concentró y se purificó por CCD preparativa para dar 130 mg (56%) como un aceite. CL/EM: t_R = 1.17 min, 596.44 $(MH)^+$.

Éster tert-butilo del ácido 3-dimetilaminometileno-4-oxo-piperidin-1-carboxílico



El éster de tert-butilo del ácido 4-oxo-piperidin-1-carboxílico (10 g, 50 mmol) se disolvió en dimetil formamida dimetilacetal (50 mL) y se calentó hasta reflujo durante 1.25 h. La solución se enfrió, se concentró y se purificó por cromatografía instantánea para dar 2.55 g (19%). Espectro de masa: 255.16 $(MH)^+$.

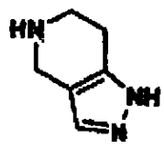
Éster de tert-butilo del ácido 1,4,6,7-tetrahidro-pirazolo[4,3-c]piridina-5-carboxílico



604 589

A una solución de éster de tert-butilo del ácido 3-dimetilaminometileno-4-oxo-piperidin-1-carboxílico (2.55 g, 10 mmol) en metanol (50 mL) se agregó hidrato de hidracina (0.61 mL, 1.25 equiv.). La solución se calentó a reflujo, inmediatamente se permitió enfriar a temperatura ambiente, y se concentró para dar 1.4 g (63%) el cual se uso sin purificación adicional. Espectro de masa: 224.11 $(MH)^+$.

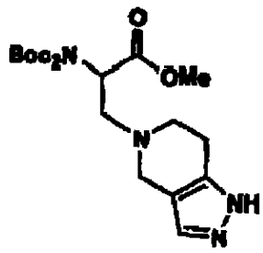
4,5,6,7-Tetrahidro-1H-pirazolo[4,3-c]piridina



El éster de tert-butilo del ácido 1,4,6,7-Tetrahidro-pirazolo[4,3-c]piridina-5-carboxílico (0.70 g, 3.1 mmol) se disolvió en ácido trifluoroacético (10 mL) a 0°C, se agitó durante 1 h, y se concentró. El residuo se disolvió en etanol y se trató con ácido clorhídrico concentrado (1 mL). La sal de bis-clorohidrato se precipito como un sólido blanco el cual se filtró para dar 510 mg (83%). La base libre se preparó como sea necesario por disolver la sal en agua, se cargó en una columna SCX, se mojó con metanol, y luego se eluyó con amonio 2 M en metanol.

590

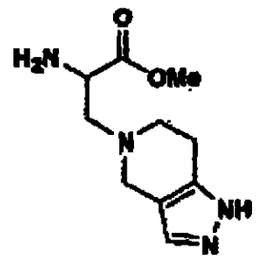
Éster de metilo del ácido (±)-2-(di-tert-butoxicarbonilamino)-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico



A una solución de 4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina (160 mg) en 2.5 mL de metanol se agregó éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-acrílico (400 mg). La reacción se concentró hasta aproximadamente 1.5 mL por aplicación de una corriente suave de nitrógeno. La solución se agitó a temperatura ambiente durante la noche. La reacción se concentró, se disolvió en acetato de etilo, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró. El residuo resultante fue lo suficientemente puro para usarse sin purificación. ^{1}H.RMN ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 2.73 (m, 3H), 2.91 (m, 1H), 3.06 (dd, J = 13.4, 8.6, 1H), 3.22 (dd, J = 13.4, 8.2, 1H), 3.54 (d, J = 13.4, 1H), 3.63 (d, J = 13.4, 1H), 3.71 (s, 3H), 5.11 (dd, J = 8.5, 5.2, 1H), 7.25 (s, 1H). Espectro de masa: 425.23 $(MH)^+$.

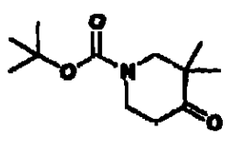
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Éster de metilo del ácido (±)-2-amino-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico



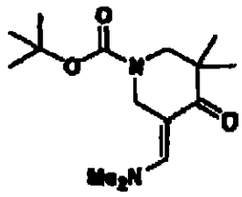
A una solución de éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (0.55 g, equiv.) en cloruro de metileno (5 mL, 0°C) se agregó ácido trifluoroacético (1.5 mL). El baño de hielo se removió y se agitó continuamente durante 2 h. La solución se concentró, se re-disolvió en metanol, y pasó en una columna de resina de intercambio de cationes fuerte. Después de mojarse con metanol, el producto se removió de la columna por elución con amonio 2 M en metanol para proporcionar el producto como esta base libre (275 mg, 95%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 2.71 (dd, J = 12.8. 8.6, 1H), 2.74-2.91 (m, 6H), 3.48 (s, 2H), 3.54 (d, J = 13.4, 1H), 3.62 (d, J = 13.4, 1H), 3.69 (dd, J = 8.2, 4.9, 1H), 3.73 (s, 3H), 7.27 (s, 1H). Espectro de masa: 225.16 $(MH)^+$.

Éster de tert-butilo del ácido 3,3-dimetil-4-oxo-piperidin-1-carboxílico



A una solución de éster de tert-butilo del ácido 4-oxo-piperidin-1-carboxílico (16 g, 80 mmol) en tetrahidrofurano (400 mL) a se agregó hidruro de sodio (4.1 g, 2.1 equiv) en 4 porciones. A esto se agregó yodometano (12.5 mL, 2.5 equiv) gota a gota. La reacción se permitió que se calentara gradualmente a temperatura ambiente y se agitó durante la noche. La reacción se concentró, se disolvió en éter de dietilo, se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró. El producto se cristalizó de pentano caliente (2X) para dar 5.9 g (32%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.09 (s, 6H), 1.47 (s, 9H), 2.47 (dd, J = 6.4, 6.4, 2H), 3.41 (m, 2H), 3.70 (m, 2H). Espectro de masa: 250.12 $(M+Na)^+$.

Éster de tert-butilo del ácido 5-dimetilaminometileno-3,3-dimetil-4-oxo-piperidin-1-carboxílico

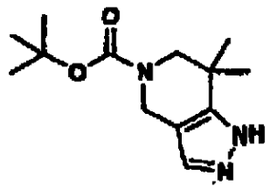


El éster tert-butilo del ácido 3,3-dimetil-4-oxo-piperidin-1-carboxílico (5 g, 22 mmol) se disolvió en dimetil formamida dimetilacetal (25 mL) y se calentó a reflujo durante 2 h. La mezcla de reacción luego se calentó a 130°C durante 1 h por medio de microondas, y se concentró para dar

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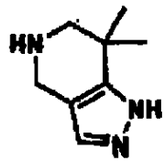
6.43 g (cuant.) como un aceite el cual se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.07 (s, 6H), 1.45 (s, 9H), 3.06 (s, 6H), 3.37 (m, 2H), 4.57 (m, 2H), 7.41 (bs, 1H).

Éster de tert-butilo del ácido 7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridina-5-carboxílico



A una solución de éster de tert-butilo del ácido 5-dimetilaminometileno-3,3dimetil-4-oxo-piperidin-1-carboxílico (6.35 g, 22 mmol) en metanol (15 mL) se agregó hidrato de hidrazina (1.2 mL, 1.1 equiv.). La solución se agitó a temperatura ambiente durante la noche y se concentró para dar 5.3 g (94%) el cual se usó sin purificación adicional. Espectro de masa: 252.19 $(MH)^+$.

7,7-Dimetil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina

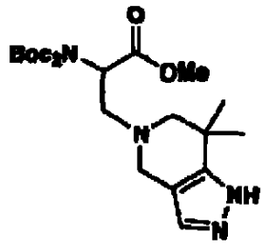


A una solución de éster de tert-butilo del ácido 7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridina-5-carboxílico (5.3 g, 21 mmol) en cloruro de metileno (10 mL) a

644 594

0°C, se agregó ácido trifluoroacético (5 mL). La reacción se permitió calentar a temperatura ambiente, se agitó 15 minutos, y se trató con ácido trifluoroacético adicional (5 mL). Después de 1 h, la reacción se concentró, se disolvió en etanol (10 mL), se enfrió para tratarse con ácido clorhídrico concentrado (3 mL), y se concentró. El sólido resultando se trituró con etanol, y se filtró para dar 3.02 g (64%) como esta sal de bis-clorohidrato. La base libre se preparó como sea necesario por disolver la sal en agua, se cargó en una columna SCX, se mojó con metanol, y luego se eluyó con amonio 2M en metanol. ^{1}H-RMN (D_2O, 500 MHz) δ 1.49 (s, 6H), 3.46 (s, 2H), 4.39 (s, 2H), 7.86 (s, 1H). Espectro de masa: 152.14 $(MH)^+$.

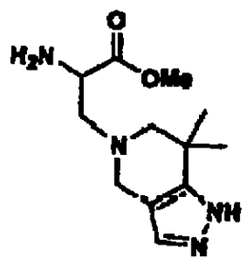
Éster de metilo del ácido (±)-2-(di-tert-butoxicarbonilamino)-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridina-5-il)-propiónico



A una solución de 7,7-dimetil-4,5,6,7-tetrahidro-1H-pirazolo[4,3-c]piridina (160 mg) en metanol (3 mL) se agregó éster de metilo del ácido 2-(di-tert-

butoxicarbonilamino)-acrílico (331 mg). Una corriente suave de nitrógeno se aplicó y la reacción se agitó durante la noche. En la mañana, el volumen se redujo gradualmente. Los últimos rastros del solvente se removieron bajo alto vacío para dar 490mg (cuant.) el cual se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.24 (s, 3H), 1.26 (s, 3H), 1.38 (s, 18H), 2.33 (d, J = 11.3, 1H), 2.57 (d, J = 11.3, 1H), 3.09 (dd, J = 13.1, 5.5, 1H), 3.15 (dd, J = 13.4, 9.5, 1H), 3.35 (d, J = 12.8, 1H), 3.57 (d, J = 12.8, 1H), 3.68 (s, 3H), 5.13 (dd, J = 9.5, 3.7, 1H), 7.16 (s, 1H). Espectro de masa: 453.30 $(MH)^+$.

Éster de metilo del ácido (±)-2-amino-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico

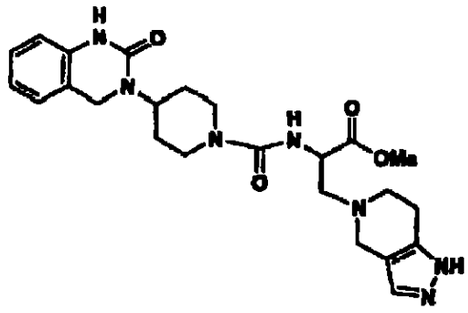


A una solución de éster de metilo del ácido 2-(di-tert-butoxicarbonilamino)-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (0.49 g, equiv.) en cloruro de metileno (5 mL, 0°C) se agregó ácido trifluoroacético (1.5 mL). El baño de hielo se removió y se

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agitó continuamente durante 2 h. La solución se concentró, se re-disolvió en metanol, y se cargó en una columna de resina de intercambio de cationes fuertes. Después de mojarse con metanol, el producto se removió de la columna por elusión con amonio 2M en metanol para proporcionar el producto como esta base libre (250 mg, 94%). ^{1}H-RMN ($CDCl_3$, 500 MHz), δ 1.27 (s, 3H), 1.28 (s, 3H), 2.41 (d, J = 11.3, 1H), 2.50 (d, J = 11.3, 1H), 2.69 (dd, J = 12.5, 7.9, 1H), 2.82 (dd, J = 12.5, 5.2, 1H), 3.45 (d, J = 12.8, 1H), 3.52 (d, J = 12.8, 1H), 3.67 (m, 1H), 3.69 (s, 3H), 7.19 (s, 1H). Espectro de masa: 253.16 $(MH)^+$.

Éster de metilo del ácido (±)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico



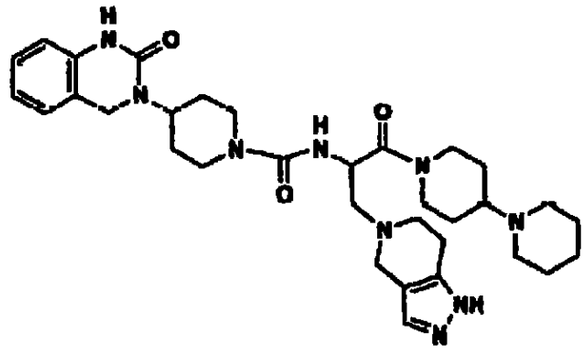
A una solución de éster de metilo del ácido 2-amino-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (260 mg, equiv.) en cloruro de metileno (2 mL, 0°C) se agregó carbonil diimidazol (188 mg, equiv).

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Después de 15 minutos, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (295 mg, 1.1 equiv) se agregó en una porción. El baño de hielo se removió y se agitó continuamente durante la noche. La reacción se concentró y se purificó por cromatografía de columna para dar 118 mg (21%). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.60-1.80 (m, 4H), 2.70-3.05 (m, 8H), 3.45 (s, 2H), 3.56 (d, J = 13.4, 1H), 3.62 (d, J = 13.4, 1H), 3.75 (s, 3H), 4.02 (d, J = 13.1, 1H), 4.10 (d, J = 12.5, 1H), 4.24 (s, 2H), 4.45-4.57 (m, 2H), 5.79 (bs, 1H), 6.68 (d, J = 7.94, 1H), 6.90 (dd, J = 7.3, 7.3, 1H), 7.00 (d, J = 7.3, 1H), 7.13 (dd, J = 7.6, 7.3, 1H), 7.25 (s, 1H), 7.82 (s, 1H). Espectro de masa: 482.27 $(MH)^+$.

Ejemplo 54

[2-[1,4']bipiperidinil-1'-il-2-oxo-1-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-ilmetil)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



GTS 593

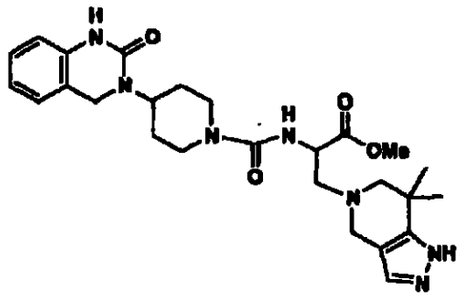
A una solución de éster de metilo del ácido 2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-3-(1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (16 mg, equiv) en metanol (0.6 mL) se agregó monohidrato hidróxido de litio (3 mg, 2.2 equiv.) en agua (0.1 mL) y se agitó durante 4 h a temperatura ambiente. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio 1 M (60 µl, 1.8 equiv), y se concentró para dar el ácido crudo el cual se usó inmediatamente sin purificación. El ácido crudo se disolvió en (0.3 mL) y se trató secuencialmente con cloruro de metileno (0.15 mL), 4-piperidil-piperidina (11 mg, 2 equiv), diisopropiletilamina (12 µl, 2 equiv), y PyBOP® (19 mg, 1.1 equiv). La solución se agitó 30 minutos y se concentró. El producto se purificó por cromatografía de columna para dar 17.6 mg (85%, 2 etapas). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.30-1.60 (m, 9H), 1.62-1.78 (m, 5H), 1.81 (bd, J = 11.0, 2H), 2.23-2.49 (m, 6H), 2.55-3.10 (m, 11H), 3.59 (d, J = 7.3, 2H), 4.00-4.20 (m, 3H), 4.23 (s, 2H), 4.50 (m, 1H), 4.63 (m, 1H), 5.03 (m, 1H), 5.71 (d, J = 7.3, 1H), 6.67 (d, J = 7.9, 1H), 6.91 (dd, J = 7.6, 7.3, 1H), 7.02 (dd, J = 7.9, 7.3, 1H), 7.14 (dd, J = 7.6, 7.6, 1H), 7.24 (s, 1H), 7.39 (s, 1H), 10.76 (bs, 1H). Espectro de masa:

619 599

618.34 $(MH)^+$.

Ejemplo 55

Éster de metilo del ácido (±)-3-(7,7-Dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

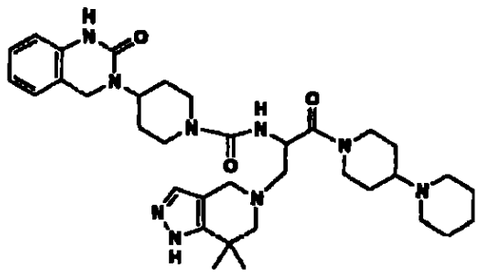


A una solución de éster de metilo del ácido 2-amino-3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-propiónico (250 mg, equiv) en tetrahidrofurano (4 mL, se le agregó diimidazol carbonilo (162 mg, 1 equiv). Después de 5 min, el baño de hielo se removió y la reacción se agitó a temperatura ambiente durante 30 min. A esto se le agregó 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (250 mg, 1.1 equiv) en una porción, y la reacción se agitó durante la noche. La reacción se concentró y purificó por cromatografía de columna para dar 228 mg (45%) ^1H RMN ($CDCl_3$, 500 MHz) δ 1.30 (s, 3H), 1.31 (s, 3H), 1.60-1.80 (m, 4H), 2.43 (d, J=11.6, 1H), 2.53 (d, J=11.3, 1H), 2.80-2.95 4H), 3.51 (dd, J=20.4, 13.1, 2H), 3.74 (s, 3H), 4.00 (d, J=13.7, 1H), 4.10 (d, J=12.2, 1H), 4.25 (dd, J=16.2, 14.4, 2H), 4.86 (m, 2H),

6.66 (d, J=7.6, 1H), 6.92 (dd, J=7.6, 7.3, 1H), 7.02 (d, J=7.3, 1H), 7.14 (dd, J=7.6, 7.6, 1H), 7.24 (s, 1H). Espectro de masa: 510.27 $(MH)^+$.

Ejemplo 56

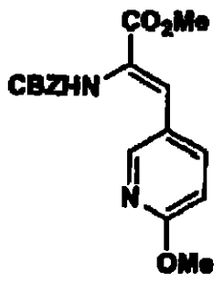
[2-[1,4']Bipiperidinil-1'-il-1-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster de metilo del ácido 3-(7,7-dimetil-1,4,6,7-tetrahidro-pirazolo[4,3-c]piridin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (20 mg, 1.0 equiv) en metanol (0.6 mL) se le agregó monohidrato de hidróxido litio (4 mg, 2.2 equiv) en agua (0.1 mL) y se agitó durante 4 h a temperatura ambiente. La solución se enfrió a 0°C, se trató con sulfato ácido de potasio 1M acuoso (75 µl, 1.8 equiv), y se concentró para dar el ácido crudo el cual se usó inmediatamente sin purificación. El ácido crudo se disolvió en dimetilformamida (0.3 mL) y se trató secuencialmente con

cloruro de metileno (0.15 mL), 4-piperidil-piperidina (13 mg, 2 equiv), diisopropiletilamina (14 µL, 2 equiv), y PyBOP® (22 mg, 1.1 equiv). La solución se agitó 1.5 h y se concentró. El producto se purificó por cromatografía de columna para dar un producto el cual se contaminó con HOBT. El HOBT se removió al pasar el producto a través de un tapón de alúmina básica, eluyendo con metanol al 10% en cloruro de metileno. La concentración dio 18.3 mg (72%, 2 etapas). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.25-1.32 (m, 6H), 1.40 (m, 4H), 1.54 (m, 5H), 1.65 (m, 4H), 1.83 (m, 2H), 2.30-2.56 (m, 8H), 2.81 (m, 4H), 3.04 (dt, J=57.1, 12.2, 1H), 3.43-3.60 (m, 2H), 4.00-4.17 (m, 2H), 4.18-4.26 (m, 3H), 4.49 (m, 1H), 4.62 (m, 1H), 5.03 (m, 1H), 5.80 (dd, J=16.8, 9.8, 1H), 6.69 (d, J=7.9, 6.90 (dd, J=7.3, 7.3, 1H), 6.99 (dd, J=7.6, 7.3, 1H), 7.13 (dd, J=7.6, 7.6, 1H), 7.19 (s, 1H), 7.66 (bd, J=12.8, Espectro de masa: 646.43 $(MH)^+$.

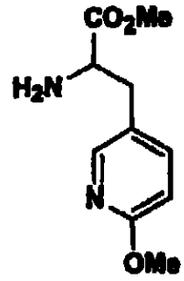
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(6-metoxi-piridin-3-il)-acrílico



A una suspensión de tert-butóxido de potasio (1.23 g,

1.5 equiv) en cloruro de metileno (70 mL, -20°C) se le agregó una solución de éster de trimetilo de N-benciloxicarbonil-α-fosfonoglicina (3.63 g, 1.5 equiv) en cloruro de metileno (15 mL). La solución resultante se agitó 5 min y se trató con el 6-metoxi-piridin-3-carbaldehído (1.0 g, 7.3 mmol) en cloruro de metileno (15 mL). Después de agitar durante 1.5 h, la reacción se entibió a 0°C y se agitó 1 h. La reacción se vació rápidamente en un embudo separador que contiene acetato de etilo y agua. La salmuera se agregó para ayudar en la separación de las capas. El acuoso se extrajo con acetato de etilo (3x) que de nuevo se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 2.63 g (cuantitativo) el cual se usó sin purificación. Espectro de masa: 343.08 $(MH)^+$.

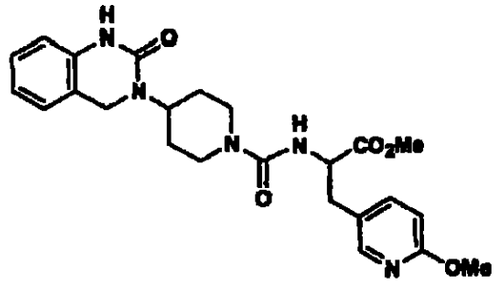
Éster de metilo del ácido (±)-2-amino-3-(6-metoxi-piridin-3-il)-propiónico



Un matraz que contiene éster de metilo del ácido 2-benciloxicarbonilamino-3-(6-metoxi-piridin-3-il)-acrílico (620 mg), paladio en carbón vegetal (10%, 100 mg), acetato de

etilo (10 mL) y metanol (20 mL) se mojó con nitrógeno, luego hidrógeno, antes de fijar finalmente un globo de hidrógeno. La reacción se dejo agitar durante la noche. El matraz se mojó con nitrógeno, se filtró a través de celite, y se concentró para dar 390 mg (cuantitativo) el cual se usó sin purificación. Espectro de masa: 211.11 $(MH)^+$.

Éster de metilo del ácido (±)-3-(6-metoxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

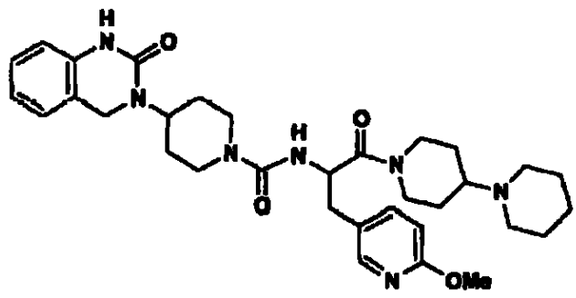


A una solución de éster de metilo del ácido 2-amino-3-(6-metoxi-piridin-3-il)-propiónico (130 mg) y diisopropiletilamina (0.3 mL) en cloruro de metileno (2 mL, 0°C) se le agregó carbonato de N,N-disuccinimidilo (158 mg). Después de 30 min, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (120 mg) en cloruro de metileno (1 mL) se agregó por medio de una cánula. La reacción se entibió a temperatura ambiente y se agitó durante la noche. La reacción se concentró y purificó por CLAR preparativa para dar 160 mg (55%). Espectro de masa: 468.19 $(MH)^+$.

621 604

Ejemplo 57

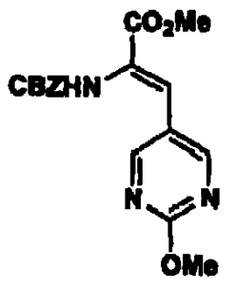
[2-[1,4']bipiperidinil-1'-il-1-(6-metoxi-piridin-3-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



A una solución de éster de metilo del ácido 3-(6-metoxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (160 mg) en metanol (6 mL) se le agregó una solución de monohidrato de hidróxido litio (29 mg) en agua (1 mL). La reacción se agitó a temperatura ambiente durante 4 h y se enfrió a 0°C. La reacción se trató con ácido clorhídrico 1N (0.6 mL), se concentró. El residuo obtenido se disolvió en cloruro de metileno (5 mL), y se trató secuencialmente con 4-piperidil-piperidina (75 mg), trietilamina (0.14 mL), y cloruro de bis-2-oxo-3-oxazolidinil)fosfínico (104 mg). La reacción se agitó durante la noche, se concentró, y purificó por CLAR preparativa para dar 94 mg (45%). CL/EM: Tr = 1.86 min., 604.51 $(MH)^+$.

605 605

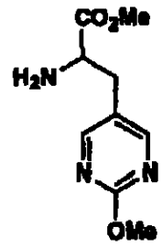
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(2-metoxi-pirimidin-5-il)-acrílico



A una suspensión de t-butóxido de potasio (1.23 g) en cloruro de metileno (70 mL, -30°C) se le agregó una solución de éster de trimetilo de N-benciloxicarbonilo (3.63 g) en cloruro de metileno (15 mL). La solución resultante se agitó 5 min y se trató con el 2-metoxi-pirimidina-5-carbaldehído (1.0 g) en cloruro de metileno (15 mL). Después de agitar durante 1.5 h, la reacción se entibió a 0°C y se agitó 1 h. La reacción se vació rápidamente en un embudo separador que contiene acetato de etilo y agua. La salmuera se agregó para ayudar en la separación de las capas. El acuoso se extrajo con acetato de etilo (3X) que de nuevo se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró. El producto crudo se recristalizó a partir del metanol caliente para dar 1.4 g de material puro. Espectro de masa: 344.10 $(MH)^+$.

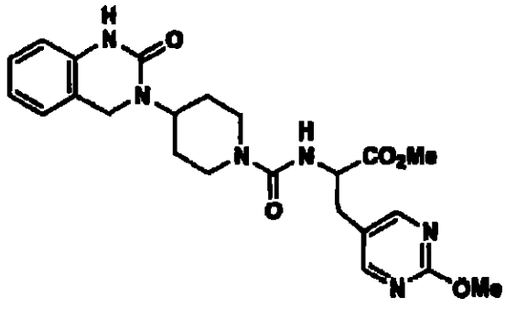
606

Éster de metilo del ácido (±)-2-amino-3-(2-metoxi-piridin-5-il)-propiónico



Un matraz que contiene éster amino (700 mg), paladio en carbón vegetal (10%, 100 mg) y metanol (20 mL) se mojó con nitrógeno, luego hidrógeno, antes de fijar finalmente un globo de hidrógeno. La reacción se dejo agitar durante la noche. El matraz se mojó con nitrógeno, se filtró a través de celite, y se concentró para dar 379 mg (88%) el cual se usó sin purificación. Espectro de masa: 212.08 $(MH)^+$.

Éster de metilo del ácido (±)-3-(2-metoxi-pirimidin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

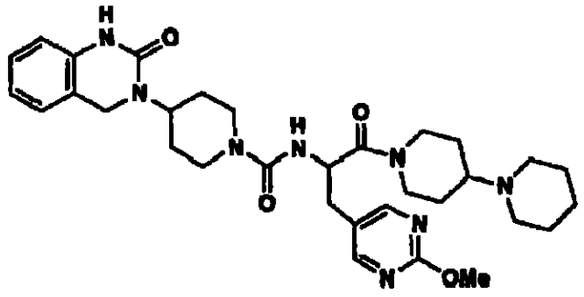


A una solución de éster de metilo del ácido 2-amino-3-(2-metoxi-pirimidin-5-il)-propiónico (125 mg) y

diisopropiletilamina (0.3 mL) en cloruro de metileno (2 mL, 0°C) se le agregó carbonato de N,N'-disuccinimidilo (155 mg). Después de 30 min, 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (120 mg) en cloruro de metileno (2 mL) se agregó por medio de una cánula. La reacción se entibió a temperatura ambiente y se agitó durante la noche. La reacción se concentró y purificó por CLAR preparativa para dar 99 mg (36%). Espectro de masa: 469.10 $(MH)^+$.

Ejemplo 58

[2-[1,4']bipiperidinil-1'-il-1-(2-metoxi-pirimidin-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

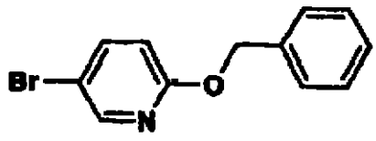


A una solución de éster de metilo del ácido 3-(2-metoxi-pirimidin-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (99 mg) en metanol (6 mL) se le agregó una solución de monohidrato de hidróxido litio (18 mg) en agua (1 mL). La reacción se agitó a temperatura ambiente durante 4 h y se enfrió a 0°C. La reacción se trató con ácido clorhídrico 1N (0.4 mL), se

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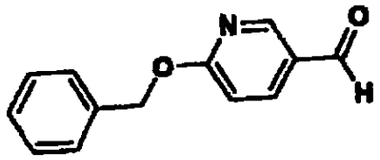
concentró. El residuo obtenido se disolvió en cloruro de metileno (3 mL), y se trató secuencialmente con 4-piperidil-piperidina (50 mg), trietilamina (88 µL), y cloruro bis-2-oxo-3-oxazolidinil)fosfínico (71 mg). La reacción se agitó durante la noche, se concentró, y purificó por CLAR preparativa para dar 103 mg (45%). CL/EM Tr = 1.23 min, 605.54 $(MH)^+$.

2-Benciloxi-5-bromo-piridina



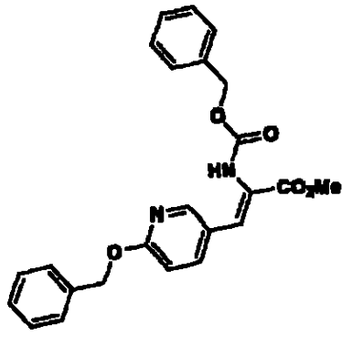
Una suspensión de 2,5-dibromopiridina (2.0 g, 8.4 mmol), dibenzo-18-corona-6 (0.14 g, .05 equiv), alcohol de bencilo (1.1 mL, 1.3 equiv), e hidróxido de potasio (1.1 g, 2.4 equiv) en tolueno (30 mL) se calentó a reflujo durante 3 h en un aparato equipado con una trampa Dean-Stark. La suspensión se enfrió, concentró, suspendió en agua, y extrajo en cloruro de metileno. Las fases orgánicas combinadas se lavaron con agua, luego salmuera, se secaron sobre sulfato de magnesio, y se concentraron para dar 1.9 g (85%) que se usó sin purificación. Espectro de masa: 264.25 $(MH)^+$.

6-Benciloxi-piridin-3-carbaldehído



A una solución de 2-benciloxi-5-bromo-piridina (1.64 g, 6.2 mmol) en tetrahidrofurano (25 mL, -78°C) se le agregó n-butillitio (2.5 M en hexano, 2.61 mL, 1.05 equiv). Después de 1 h a -78°C, dimetilformamida (0.97 mL, 2 equiv) se agregó y la mezcla se agitó durante 30 min. La reacción se vació rápidamente en una solución agitada de bicarbonato de sodio acuoso al 5% (50 mL) y se extrajo con éter de dietilo (3x). El etéreo se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 1.16 g (cuantitativo) que se usó sin purificación. Espectro de masa: 186.34 $(MH)^+$.

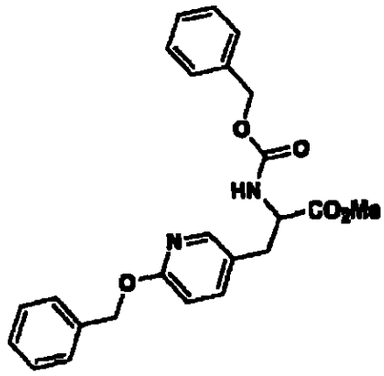
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-acrílico



630 610

A una suspensión agitada de tert-butóxido de potasio (0.440 g, 1.7 equiv) en cloruro de metileno (25 mL) a -20°C se le agregó éster de trimetilo N-benciloxicarbonil-α-fosfonoglicina (1.3 g, 1.7 equiv) en cloruro de metileno (5 mL). La solución resultante se agitó durante 5 min y se trató con el 6-benciloxi-piridin-3-carbaldehído (0.49 g, 2.28 mmol) en cloruro de metileno (5 mL). La reacción se agitó a -20°C durante 1 h, se permitió para entibiar gradualmente a 0°C, y se vació en un embudo separador que contiene agua y éter de dietilo. La reacción se extrajo con éter de dietilo (2x), se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 0.98 g (cuantitativo) como un aceite que se usó sin purificación. Espectro de masa: 419.32 $(MH)^+$.

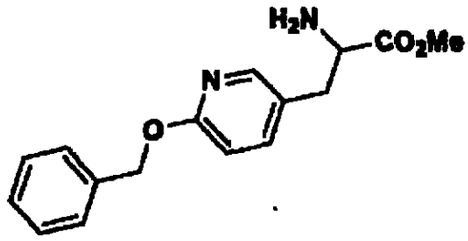
Éster de metilo del ácido (±)-2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-propiónico



Un matraz se cargó con éster de metilo del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-acrílico (0.50 g, 1.2 mmol), catalizador Wilkinson (200 mg, 0.2

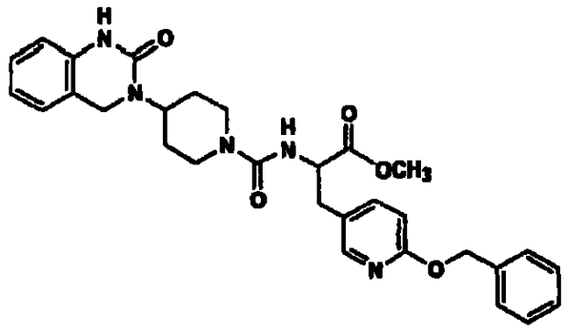
equiv), metanol (5 mL), y tolueno (3 mL). El matraz se mojó con nitrógeno, luego hidrógeno, se calentó a 35°C, y se dejo agitar bajo una atmósfera de hidrógeno durante 4 días. La reacción se mojó con nitrógeno, se diluyó con metanol, se filtró, y se concentró para proporcionar el producto crudo el cual se purificó por cromatografía de columna para dar 145 mg (29%).

Éster de metilo del ácido (±)-2-amino-3-(6-benciloxi-piridin-3-il)-propiónico



A una solución agitada de éster de metilo del ácido 2-benciloxicarbonilamino-3-(6-benciloxi-piridin-3-il)-propiónico (130 mg, 0.31 mmol) en cloruro de metileno (5 mL, se le agregó yoduro de trimetilsililo (44 µL, 1.0 equiv). El baño de hielo se removió y se agitó continuamente durante 1 h. La reacción se vació en bicarbonato de sodio saturado, se extrajo con acetato de etilo (3x), se lavó con salmuera, se secó sobre sulfato de magnesio, y se concentró para dar 81 mg (91%) que se usó sin purificación. Espectro de masa: 287.37 $(MH)^+$.

Éster de metilo del ácido (±)-3-(6-benciloxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

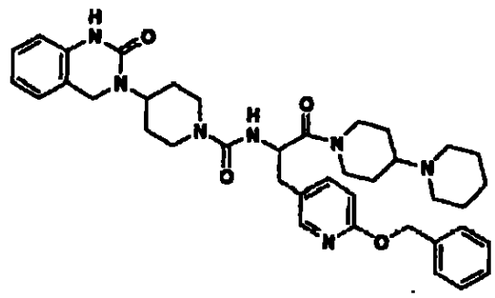


A una solución agitada de éster de metilo del ácido 2-amino-3-(6-benciloxi-piridin-3-il)-propiónico (60 mg, 0.21 mmol) en cloruro de metileno (1 mL, 0°C) se le agregó diimidazol carbonilo (34 mg, 1.0 equiv.). Después de 15 min, una solución de 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (58 mg, 1.2 equiv.) en cloruro de metileno (0.5 mL) se agregó por medio de una cánula. El baño de hielo se removió y continuó la agitación durante la noche. La reacción se concentró y purificó por cromatografía de columna para dar 59 mg (52%). Espectro de masa: 544.49 $(MH)^+$.

613

Ejemplo 59

[1-(6-Benciloxi-piridin-3-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

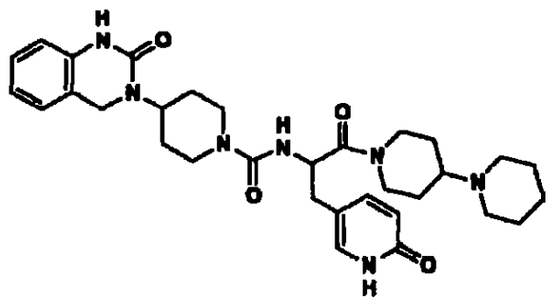


A una solución agitada de éster de metilo del ácido 3-(6-benciloxi-piridin-3-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (59 mg, 0.11 mmol) en metanol (3 mL) se agregó una solución de monohidrato de hidróxido litio (9.1 mg, 2 equiv) en agua (0.5 mL). La reacción se agitó 2 h a temperatura ambiente, se enfría hasta 0°C, se apaga por la adición de ácido clorhídrico 1N (0.15 mL), y se concentró. El producto crudo se usó sin purificación. El ácido crudo se disolvió en cloruro de metileno (2 mL, 0°C) y se trata secuencialmente con 4-piperidino-piperidina (34 mg, 1.8 equiv), trietilamina (35 µL, 2.3 equiv.), y cloruro bis-2-oxo-3-oxazolidinil)fosfínico (34 mg, 1.2 equiv). El baño de

hielo se removió y la reacción se dejo agitar durante la noche. La reacción se concentró y purificó por CCD preparativa para dar 30.3 mg (41%). CL/EM: Tr = 1.49 min, 680.29 $(MH)^+$.

Ejemplo 60

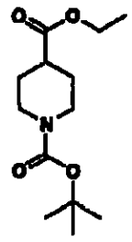
[2-[1,4']Bipiperidinil-1'-il-2-oxo-1-(6-oxo-1,6-dihidro-piridin-3-ilmetil)-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Un matraz se cargó con [1-(6-benciloxi-piridin-3-ilmetil)-2-[1,4']bipiperidinil-1'-il-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico (27 mg, 0.04 mmol), paladio en carbón vegetal (10%, 4 mg), y metanol (1 mL). El matraz se mojó con nitrógeno, luego hidrógeno, y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. El matraz se mojó con nitrógeno, y la reacción se filtró a través de celite para dar 22.1 mg (94%). CL/EM: Tr = 0.93 min, 590.32 $(MH)^+$.

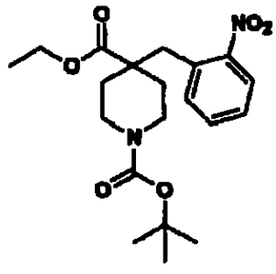
615

Éster de 4-etil del éster de 1-tert-butilo del ácido piperidin-1,4-dicarboxílico



A una solución de isonipecotato de etilo (5.00 g, 0.032 mol) y trietilamina (4.9 mL, 0.035 mmol) en diclorometano (25 mL) a 0°C se le agregó lentamente una solución de di-tert-butildicarbonato (7.2 g, 0.033 mol) en diclorometano (25 mL). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se lavó con sulfato ácido de potasio tres veces y con salmuera una vez. El extracto orgánico se secó sobre sulfato de sodio anhidro, se filtró y concentró in vacuo para dar el producto deseado (8.23 g, 100%) como aceite incoloro. ^{1}H RMN (C_6D_6, 500 MHz) δ 3.88 (q, J= 7.5 Hz, 2H), 2.52 (m, 1H), 1.60-1.48 (m, 8H), 1.42 (s, 9H), 0.92 (t, 3H). Espectro de masa: 280.44 $(M+Na)^+$.

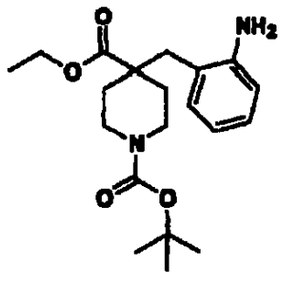
Éster de 4-etilo del éster 1-tert-butilo del ácido 4-(2-nitro-bencil)-piperidin-1,4-dicarboxílico



636 616

A una solución de éster de 4-etilo del éster 1-tert-butilo del ácido piperidin-1,4-dicarboxílico (8.23 g, 0.032 mol) en tetrahidrofurano (85 mL) se le agregó lentamente una solución de bis(trimetilsilil)amida de sodio (44 mL, 0.044 mol). Después de que la mezcla resultante se ha agitado a -78°C durante 1 h, una solución de bromuro de 2-nitrobencilo (8.21 g, 0.038 mol) se agregó. La mezcla de reacción se permitió hasta entibiar a temperatura ambiente y se agitó durante la noche. Esto se concentró luego y el residuo se dividió entre agua y acetato de etilo. El extracto orgánico se lavó con salmuera, se secó sobre sulfato de magnesio anhidro, se filtró, y se concentró bajo vacío. El producto final se purificó a partir de la mezcla de reacción de complejo por vía de cromatografía de columna en gel de sílice (eluyente-hexanos-acetato de etilo 4:1) para dar el producto deseado (1.61 g, 13%) como aceite café. Espectro de masa: 415.38 $(M+Na)^+$.

Éster de 4-etilo del éster 1-tert-butilo del ácido 4-(2-amino-bencil)-piperidin-1,4-dicarboxílico

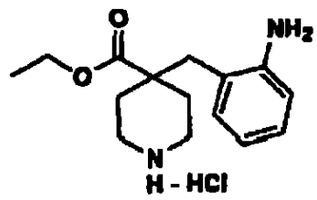


Una mezcla del éster 4-etilo del éster 1-tert-butilo del

637 617

ácido 4-(2-nitro-bencil)-piperidin-1,4-dicarboxílico (1.61 g, 4.102 mmol) y paladio en carbón vegetal al 10% (0.10 g) en etanol (190 mL) se hidrogenó a 50 psi (3.515 Kg/cm^2) durante la noche. La mezcla resultante se filtró a través de un tapón de celite, y el filtrado se concentró bajo vacío para proporcionar el producto deseado (1.29 g, 99%) como aceite incoloro. Espectro de masa: 363.45 $(MH)^+$.

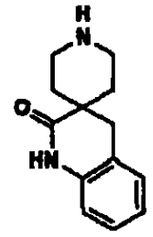
Clorohidrato del éster de etilo del ácido 4-(2-amino-bencil)-piperidin-4-carboxílico



A una solución de éster de 4-etilo del éster 1-tert-butilo del ácido 4-(2-amino-bencil)-piperidin-1,4-dicarboxílico (1.29 g, 4.102 mmol) en diclorometano (15 mL) se le agregó una solución 4.0 M de cloruro de hidrógeno en dioxano (5 mL). La solución resultante se agitó a temperatura ambiente durante la noche. La concentración de la solución bajo vacío proporcionó el compuesto del título (1.23 g, 100%) como sólido blanco, que se usó en la siguiente etapa sin purificación. Espectro de masa: 263.40 $(MH)^+$.

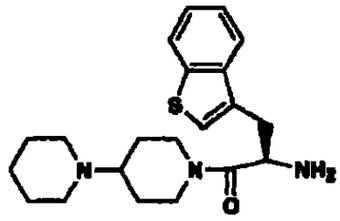
617/618

3,4-Benzo-2,9-diazaespiro[5.5]undeca-1-ona



Una solución de clorohidrato de éster de etilo del ácido 4-(2-amino-bencil)-piperidin-4-carboxílico (1.23 g, 4.102 mmol) se disolvió en metanol y la solución resultante se agitó a temperatura ambiente durante la noche. La solución se diluyó a la mitad con agua y pasó a través de un tapón corto de la forma de hidróxido de resina de intercambio de iones AG® 1-X2 (100-200 malla), eluyendo con metanol acuoso al 50%. La evaporación de las fracciones colectadas dio el producto deseado (0.89 g, 100%) como sólido blanco. ^{1}H-RMN (CD_3OD, 500 MHz) 7.23 (m, 2H), 7.05 (d, J= 7.5 Hz, 1H), 6.89 (d, J= 8.0 Hz, 1H), 3.46-3.41 (m, 2H), 3.34-3.30 (m, 2H), 2.14-2.09 (m, 2H), 1.73-1.67 (m, 4H). Espectro de masa: 217.46 $(MH)^+$.

(R)-2-Amino-3-benzo[b]tiofen-3-il-1-[1,4']bipiperidinil-1'-il-propan-1-ona, clorohidrato



A una solución bien agitada de ácido 3-benzo[b]tiofen-3-il-

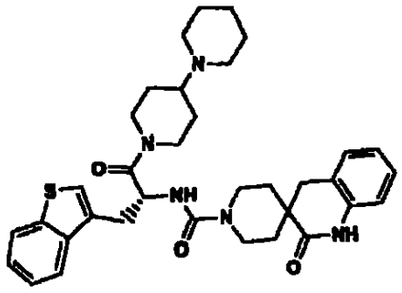
639 619

(2R)-2-tert-butoxicarbonilamino-propiónico (1.0 g, 3.1 mmol) en cloruro de metileno (30 mL) a temperatura ambiente se le agregó (573 mg, 3.4 mmol), trietilamina (1.3 mL, 9.3 mmol) seguido por 3-(dietoxifosforiloxi)-1,2,3-benzotriazin-4(3H)-ona (1.02 g, 3.4 mmol). Después de 3 h, la mezcla de reacción se trató con carbonato ácido de sodio acuoso (15 mL), salmuera (20 mL) y se secó (sulfato de sodio). La mezcla cruda se purificó por la cromatografía instantánea usando metanol al 5% en cloruro de metileno para dar éster de tert-butilo del ácido (1R)-1-benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-carbámico en 82% de rendimiento. Éster de tert-butilo del ácido (1R)-1-Benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-carbámico (1.2 g, 2.54 mmol) en cloruro de metileno (5 mL) se agregó a una solución saturada de cloruro de hidrógeno en dioxano (20 mL) y se agitó durante 2 h. Los solventes se removieron para dar (2R)-2-amino-3-benzo[b]tiofen-3-il-1-[1,4']bipiperidinil-1'-il-propan-1-ona, diclorohidrato en 98% de rendimiento. ^{1}H-RMN (500 MHz, CD_3OD): δ 7.98-7.88 (m, 2 H), 7.55-7.40 (m, 3 H), 4.85-4.83 (m, 1H), 3.66-2.68 (m, 9 H), 1.92-1.44 (m, 12 H). Espectro de masa: 372 $(MH)^+$.

610 620

Ejemplo 61

(1-Benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del ácido (R)-1-Oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-eno-9-carboxílico



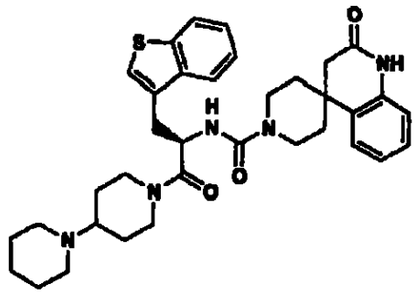
A una solución de 2-amino-3-benzo[b]tiofen-3-il-1-[1,4']bipiperidinil-1'-il-propan-1-ona (50.0 mg, 0.135 mmol) en 1,2-dicloroetano (1.5 mL) se le agregaron carbonato N,N'-disuccinimidilo (34.6 mg, 0.135 mmol) y amina de diisopropiletilo (0.09 mL, 0.500 mmol). La solución resultante se agitó durante 1 h, punto en el cual 3,4-benzo-2,9-diazaespiro[5.5]undeca-1-ona (30.4 mg, 0.140 mmol) se agregó. La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró. La purificación se realizó por vía de CLAR preparativa de fase inversa para dar el producto deseado (75.5 mg, 77%) como aceite café. ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.92-7.85 (m, 2H), 7.44-7.34 (m, 3H), 7.21-7.16 (m, 2H), 7.00 (t, J= 7.0 Hz, 1H), 6.86 (t, J=8.5 Hz, 1H), 5.15-5.02 (m, 1H), 4.72-4.45 (m, 1H), 3.95-3.20 (m, 8H), 3.18-2.92 (m, 4H), 2.92-2.75 (m, 2H),

621

2.75-2.63 (m, 1H), 2.40-2.30 (m, 1H), 2.08-1.64 (m, 8H), 1.58-1.20 (m, 6H). Espectro de masa: 614.37 $(MH)^+$.

Ejemplo 62

N-[(1R)-1-(Benzo[b]tien-3-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-3',4'-dihidro-2-oxoespiro-[piperidin-4,4'(1H)-quinolina]-1-carboxamida

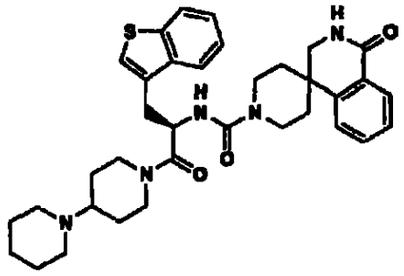


Se preparó como se describe por (1-benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-eno-9-carboxílico a partir de 3',4'-dihidro-2-oxoespiro-[piperidin-4,4'(1H)-quinolina (M.S. Chambers, et al., J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ - 0.35 (1H, m), 0.79 (1H, m), 1.2-2.1 (12H, m), 2.22 (5H, m), 2.38 (2H, m), 2.74 (2H, Abq), 3.19 (3H, m), 3.33 (2H, m), 3.65 (1H, d), 3.80 (1H, m), 3.93 (1H, t), 4.49 (1H, d), 5.31 (1H, t), 5.96 (1H, t), 6.89 (1H, d), 7.05 (1H, t), 7.18 (1H, d), 7.26 (1H, m), 7.33 (1H, m), 7.40 (1H, m), 7.78 (1H, m),

7.96 (1H, Abq), 9.01 (1H, brs), 9.17 (1H, brs). Espectro de masa: 614.36 $(MH)^+$.

Ejemplo 63

N-[(1R)-1-(Benzo[b]tien-3-ilmetil)-2-[1,4bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-1-oxoespiro-[piperidin-4,4'(1H)-isoquinoina]-1-carboxamida

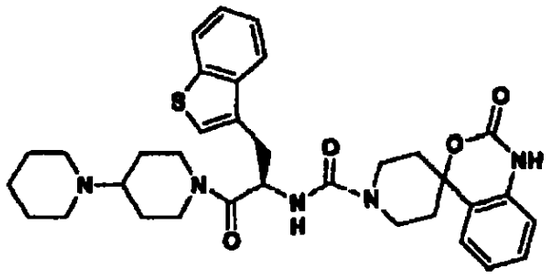


Se preparó como se describe por (1-benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxo-etil)-amida del ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-eno-9-carboxílico a partir de 2',3'-dihidro-1-oxoespiro-[piperidin-4,4'-(1H)-isoquinolina (M.S. Chambers, et al., J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 0.01 (1H, m), 0.78 (1H, m), 1.1-2.0 (12H, m), 2.15-2.30 (5H, m), 2.74 (1H, t), 3.0-3.6 (9H), 3.89 (2H, m), 4.46 (1H, d), 5.29 (1H, m), 5.62 (1H, d), 6.47 (1H, brs), 7.38 (5H, m), 7.51 (1H, m), 7.77 (1H, m), 7.85 (1H, m), 8.11 (1H, d). Espectro de masa: 614.42 $(MH)^+$.

649 623

Ejemplo 64

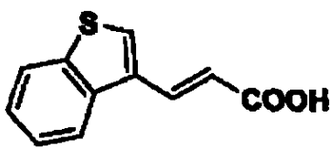
N-[(1R)-1-(Benzo[b]tien-3-ilmetil)-2-[1,4'-bipiperidin]-1'-il-2-oxoetil]-1,2-dihidro-2-oxoespiro-[4H-3,1-benzoxazina-4,4'-piperidina]-1'-carboxamida



Se preparó como se describe por (1-benzo[b]tiofen-3-ilmetil-2-[1,4']bipiperidinil-1'-il-2-oxoetil)-amida del ácido (R)-1-oxo-3,4-benzo-2,9-diaza-espiro[5.5]undec-3-eno-9-carboxílico a partir de 1,2-dihidro-2-oxoespiro-[4H-3,1-benzoxazina-4,4'-piperidina (se preparó como se describe en Takai, et al.; Chem. Pharm. Bull. 1985, 33, 1129-1139) para dar el compuesto del título (76%). Espectro de masa: 616 $(MH)^+$. Rf = 1.42.

Intermediarios de Succinato y Ejemplos

Ácido 3-Benzo[b]tiofen-3-il-acrílico

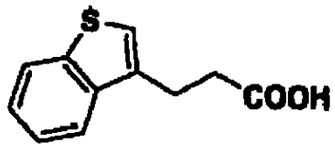


Una suspensión de 1-benzotiofeno-3-carbaldehído (4.9 g,

Gott/624

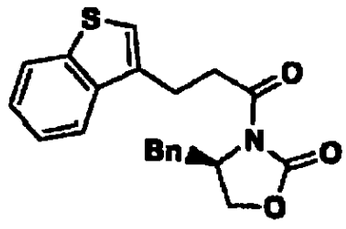
0.03 mol), ácido malónico (6.6 g, 0.06 mol) y piperidina (1 mL) en 100 mL piridina anhidro se calentó a 110°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y el solvente se removió in vacuo. El residuo se tomó en 100 mL de agua y ácido clorhídrico 1 N se le agregó para ajustar el pH de esta solución a ca. 3. La suspensión se filtró y el sólido amarillo se colectó, lavó con agua (3 x 50 mL) y se concentró in vacuo para dar el producto indicado con 95% de pureza (5.65 g, 91%).

Ácido 3-Benzo[b]tiofen-3-il-propiónico



Una suspensión de ácido 3-benzo[b]tiofen-3-il-acrílico: (5.6 g, 0.027 mol) y Pd/C 10% (600 mg) en 1:1 metanol/acetato de etilo (50 mL) se hidrogenó en un aparato Parr a 50 psi (3.515 Kg/cm^2) durante la noche. La mezcla se filtró y se concentró para dar el producto crudo sin purificación adicional (ca. 100% conversión). Espectro de masa: 205 $(MH)^-$.

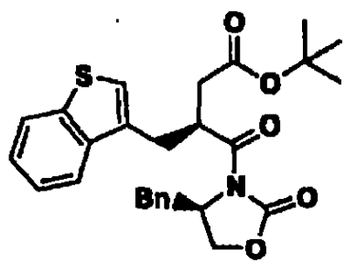
3-(3-Benzo[b]tiofen-3-il-propionil)-4(R)-bencil-oxazolidin-2-ona



691/625

A una solución de ácido 3-benzo[b]tiofen-3-il-propiónico (2.1 g, 0.010 mol), trietilamina (4.12 g, 0.040 mol) en tetrahidrofurano anhidro (100 mL) a 0°C se agregó cloruro de pivalilo (1.38 mL, 0.011 mol). Después de agitar durante 1.5 h a 0°C, cloruro de litio (0.475 g, 0.011 mol) y (R)-4-bencil-2-oxazolidinoa (1.988 g, 0.011 mol) se agregaron. La mezcla de reacción se permitió hasta entibiar a temperatura ambiente y se agitó durante la noche. Luego la mezcla se lavó con agua (3 x 150 mL). La capa orgánica se separó, secó, y evaporó para dar el producto crudo. El producto del título se obtuvo como un aceite café (90%) por cromatografía instantánea en gel de sílice eluyendo con cloruro de metileno 100%. Este compuesto se usó inmediatamente en el siguiente procedimiento.

Éster de tert-butilo del ácido 3(S)-Benzo[b]tiofen-3-ilmetil-4-(4-bencil-2-oxo-oxazolidin-3-il)-4-oxo butírico

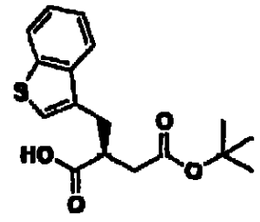


A una solución de 3-(3-benzo[b]tiofen-3-il-propionil)-4-bencil-oxazolidin-2-ona (3.35 g, 9.18 mmol) en tetrahidrofurano anhidro 100 mL a -78°C se le agregó litio

6446 626

diisopropil amida en tetrahidrofurano (6.1 mL, 11.01 mmol) y la mezcla de reacción se agitó durante 30 min. Siguiendo la adición de bromoacetato de t-butilo (1.62 mL, 11.01 mmol) a -78°C, la mezcla se agitó durante la noche mientras esto se permitió hasta entibiar a temperatura ambiente. El solvente se evaporó y el residuo se diluyó con acetato de etilo. La capa orgánica se lavó con agua (3 x 100 mL), se secó, se filtró, y se concentró para dar el producto crudo. El producto del título se obtuvo por filtración a través de una almohadilla de sílice, eluyendo con cloruro de metileno (49%).

Ácido 2(S)-Benzo[b]tiofen-3-ilmetil-succínico, éster de 4-tert-butilo

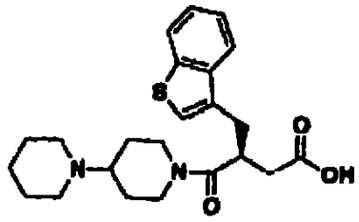


A una solución agitada de éster de tert-butilo del ácido 3-benzo[b]tiofen-3-ilmetil-4-(4-bencil-2-oxo-oxazolidin-3-il)-4-oxobutírico (2.15 g, 4.49 mmol) en tetrahidrofurano (50 mL) y agua (30 mL) a 0°C se le agregó peróxido de hidrógeno acuoso 30% (1 mL) seguido por hidróxido de litio (0.2155 g, 8.98 mmol). La mezcla de reacción se agitó durante la noche.

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El tetrahidrofurano se removió in vacuo y la solución resultante se hizo ácida con ácido cítrico al 10%, y se extrajo con acetato de etilo (3 x 50 mL). La capa orgánica se lavó con solución de bisulfito de sodio, se secó y se concentró para dar el producto del título.

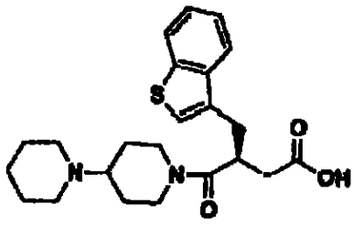
Éster de tert-butilo del ácido 3(S)-Benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico



Una solución de éster de 4-tert-butilo del ácido 2-benzo[b]tiofen-3-ilmetil-succínico (1.8420 g, 5.76 mmol), piperidilpiperidina (1.2240 g, 7.28 mmol) y trietilamina (0.7353 g, 7.28 mmol) en cloruro de metileno 100 mL se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 1.8953 g, 6.34 mmol). La mezcla se agitó durante la noche y luego se lavó con agua (3 x 40 mL). La capa orgánica se secó, se filtró, y se concentró in vacuo para dar el producto crudo. Este se purificó además por la cromatografía instantánea en gel de sílice, eluyendo con amoniaco en metanol 2 M 0-10%/cloruro de metileno, para dar el producto deseado. Este producto se

llevó a cabo sin purificación adicional.

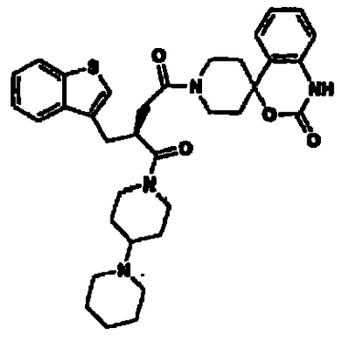
Ácido 3(S)-Benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico



Una solución de éster de tert-butilo del ácido 3-benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico en cloruro de metileno 15 mL se trató con ácido trifluoroacético (3 mL) y la mezcla de reacción se agitó durante la noche a temperatura ambiente. El solvente se evaporó para dar la sal de trifluoroacetato correspondiente del producto del título (99%).

Ejemplo 65

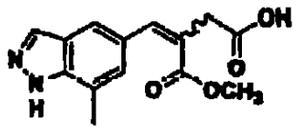
1-[1,4']Bipiperidinil-1'-il-2-(3(S)-Benzo[b]tiofen-3-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona



649 629

Una solución de ácido 3-benzo[b]tiofen-3-ilmetil-4-[1,4']bipiperidinil-1'-il-4-oxo-butírico (25.0 mg, 0.060 mmol), 1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazina-4'4-piperidina (15.7 mg, 0.072 mmol) y trietilamina (7.3 mg, 0.072 mmol) en cloruro de metileno 5 mL a temperatura ambiente se trató con 3-(doetoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 21.5 mg, 0.072 mmol). La solución se agitó durante la noche y luego se lavó con agua (3 x 5 mL). La capa orgánica se secó, concentró, y el producto crudo se purificó por la cromatografía instantánea en gel de sílice, eluyendo con amonio en metanol 2M 0-10%/cloruro de metileno, para dar el producto deseado en 60% de rendimiento. CL/EM: tR = 1.34 min, 615.45 $(MH)^+$.

Éster de 1-metilo del ácido 2-(7-metil-1H-indazol-5-ilmetileno)-succínico

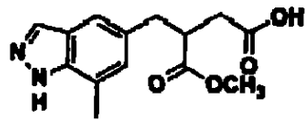


A una mezcla de 7-metil indazol aldehído (0.2619 g, 1.64 mmol) y éster dibásico DBE-4 (succinato de dimetilo) (0.32 mL, 2.45 mmol) en t-butanol (20 mL) se le agregó t-butóxido de potasio (0.4036 g, 3.60 mmol). La mezcla de reacción se calentó a 50°C durante 2 h bajo nitrógeno. Después de 16 h adicionales a temperatura ambiente, el

630 630

solvente se removió in vacuo y el residuo se tomó en agua (100 mL) y se extrajo con acetato de etilo (3 x 50 mL). La capa acuosa se hizo ácida con ácido clorhídrico 1 N a un pH 3~4 y se extrajo con acetato de etilo (3 x 50 mL). La solución de acetato de etilo combinado se secó y concentró in vacuo para dar el producto crudo como un sólido amarillo (99%, isómero cis/trans aproximadamente 40:60). La mezcla cruda se llevó a la siguiente etapa sin purificación adicional. Espectro de masa: 275 $(MH)^+$.

Éster de 1-metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-succínico

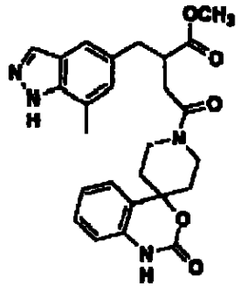


Una suspensión de éster 1-metilo del ácido 2-(7-metil-1H-indazol-5-ilmetileno)-succínico (0.4440 g, 1.62 mmol) y 10% Pd/C (0.04 g) en acetato de etilo (15 mL) y metanol (5 mL) se hidrogenó en un aparato Parr durante la noche a 50 psi (3.515 Kg/cm^2). La mezcla de reacción se filtró a través de una almohadilla de celite y el filtrado se evaporó para dar el producto deseado como un sólido amarillo (100%). Espectro de masa: 277 $(MH)^+$.

654 631

Ejemplo 66

éster de metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico



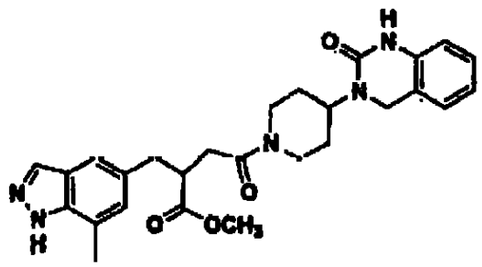
Una solución de éster de 1-metilo del ácido 2-(7-metil-1H-indazol-5-ilmetil)-succínico (0.2253 g, 0.82 mmol), 1,2-dihidro-2-oxoespiro-4H-3,1-dihidro-benzoxazina-4'4-piperidina (0.1938 g, 0.89 mmol) y trietilamina (0.099 g, 0.98 mmol) en cloruro de metileno (15 mL) se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 0.2685 g, 0.90 mmol). La mezcla se agitó durante la noche y luego se lavó con agua (3 x 5 mL). La capa orgánica se secó, y se concentró in vacuo. El residuo se purificó por la cromatografía instantánea en gel de sílice, eluyendo con amoniaco en metanol 2M 0-10%/cloruro de metileno, para proporcionar el producto deseado (53%). CL/EM: t_R= 1.40 min, 477.28 $(MH)^+$.

Preparado similarmente:

655 632

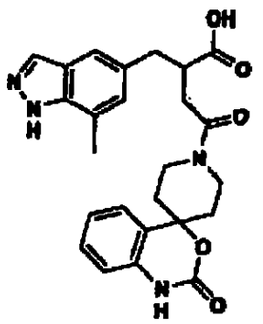
Ejemplo 67

Éster de metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico



^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.98 (1H, m), 7,90 (1H, m), 7.35-6.89 (4H, m), 6.72 (1H, m), 4.71 (1H, m), 4.57 (1H, m), 4.27 (1H, s), 4.22 (1H, m), 3.85 (1H, m), 3.65 (3H, m), 3.30 (1H, m), 3.11 (2H, m), 2.83 (2H, m), 2.81-2.54 (4H, m), 2.35 (1H, m), 1.73-1.67 (4H, m). Espectro de masa: 490.32 $(MH)^+$.

Ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico

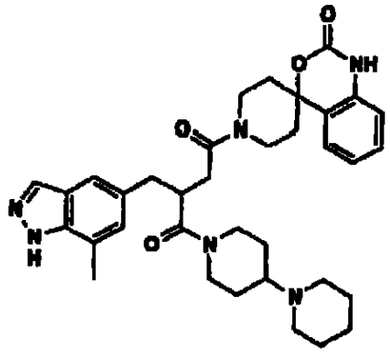


655 633

Una solución de éster de metilo del ácido 2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico (0.1911 g, 0.40 mmol) e hidróxido de litio (19.3 mg, 0.80 mmol) en tetrahidrofurano (10 mL) y agua (8 mL) se agitó durante la noche a temperatura ambiente. La mezcla de reacción se hizo ácida con ácido clorhídrico 1N a ca. pH 1 y se concentró para remover tetrahidrofurano in vacuo para proporcionar un precipitado sólido blanco que se colectó por filtración. El sólido se lavó dos veces con cantidades pequeñas de agua y se secó in vacuo durante la noche (100%). Espectro de masa: 477 $(MH)^+$.

Ejemplo 68

(±)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona



Una solución de 2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-

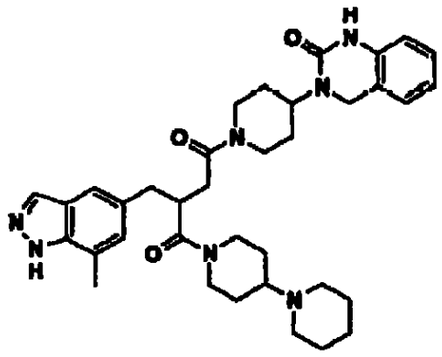
634

4,4'-piperidinil]-butírico (0.020 g, 0.04 mmol), piperidilpiperidina (0.0087 g, 0.05 mmol) y trietilamina (0.09 g, 0.08 mmol) en cloruro de metileno (5 mL) a temperatura ambiente se trató con 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 0.0155 g, 0.05 mmol). La mezcla se agitó durante la noche y luego se lavó con agua (3 x 5 mL). La capa orgánica se secó y los solventes se removieron in vacuo. El producto crudo se purificó por CCD preparativa en gel de sílice (hidróxido de amonio 2M 10%/metanol en cloruro de metileno) para dar el producto deseado (36%). CL/EM: Tr = 1.18 min, 613.47 $(MH)^+$.

Preparado similarmente:

Ejemplo 69

(±)-1-[1,4']-Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



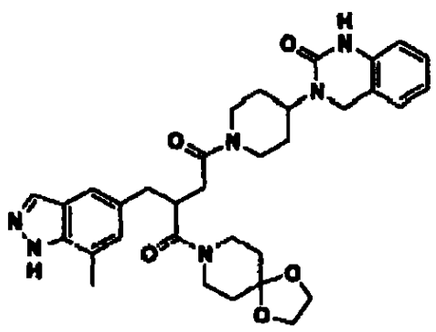
^{1}H-RMN (400 MHz, $CDCl_3$) δ 7.99(1H, m), 7.62 (1H, m), 7.38

635

(1H, m), 7.14 (1H, m), 7.04-6.90 (3H, m), 6.70 (2H, d, J=8.0 Hz), 4.70-4.58 (3H, m), 4.24 (2H, m), 4.00 (2H, m), 3.70 (1H, m), 3.18-2.72 (5H, m), 2.64-2.22 (8H, m), 2.18-0.82 (17H, m). Espectro de masa: 626.34 $(MH)^+$.

Ejemplo 70

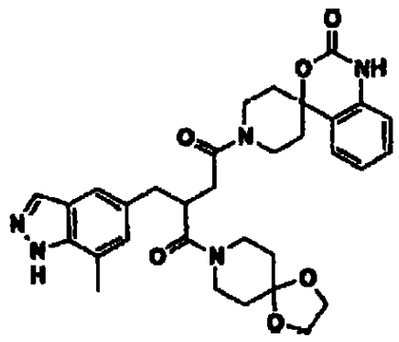
(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.06 (1H, s), 7.75 (1H, m), 7.36 (1H, m), 7.14 (1H, m), 7.01-6.79 (3H, m), 6.70 (1H, m), 4.70-4.49 (2H, m), 4.23 (2H, m), 3.98 (1H, m), 3.87 (3H, m), 3.65-3.44 (4H, m), 3.26 (1H, m), 3.10-2.88 (3H, m), 2.75 (1H, m), 2.51 (3H, s), 2.35 (1H, m), 2.00 (1H, m), 1.70-1.00 (9H, m). Espectro de masa: 601.38 $(MH)^+$.

Ejemplo 71

(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona

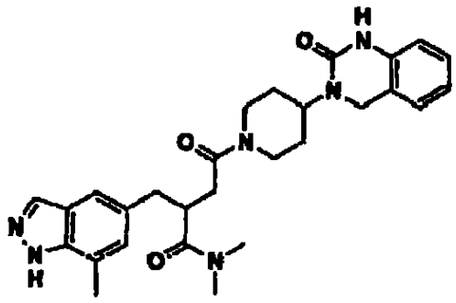


^{1}H-RMN (400 MHz, $CDCl_3$) δ 9.27 (1H, m), 8.00 (1H, s), 7.37 (1H, m), 7.23 (1H, m), 7.10-6.99 (3H, m), 6.87 (1H, m), 4.54 (1H, m), 3.97-3.50 (10H, m), 3.30 (1H, m), 3.16-2.76 (4H, m), 2.53 (3H, s), 2.35 (1H, m), 2.20-1.00 (9H, m).

Espectro de masa: 588.36 $(MH)^+$.

Ejemplo 72

(±)-N,N-Dimetil-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida

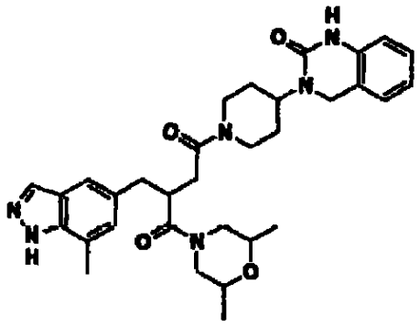


CL/EM: t_R= 1.36 min, 525.35 $(M+Na)^+$.

637 637

Ejemplo 73

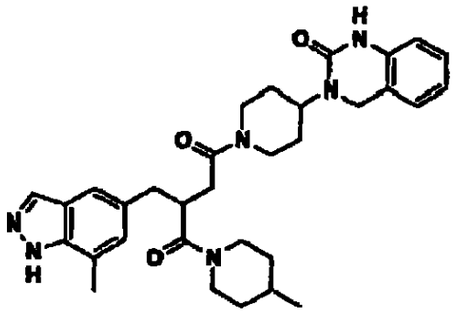
(±)-1-(2,6-Dimetil-morfolin-4-il)-2-(7-metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



CL/EM : t_R= 1.41 min, 573.39 $(MH)^+$.

Ejemplo 74

(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-(4-metil-piperidin-1-il)-4-[4-(2-oxo-1,4-diona

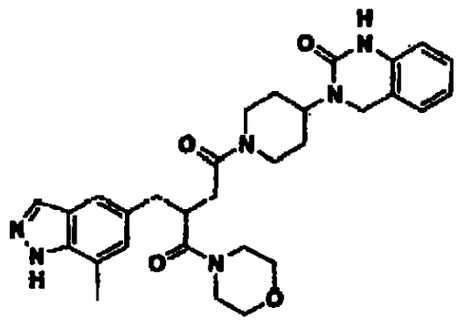


^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.06 (1H, b), 7.60-6.73 (7H, m), 4.71 (1H, m), 4.54 (2H, m), 4.26 (2H, m), 4.05-3.89 (2H, m), 3.65 (1H, m), 3.09-2.81 (4H, m), 2.61 (3H, s), 2.41 (2H, m), 1.76-0.51 (15H, m). Espectro de masa: 557.38 $(MH)^+$.

651 638

Ejemplo 75

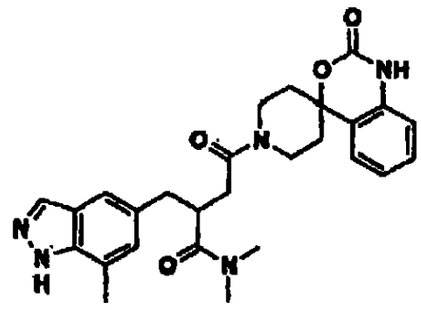
(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-morfolin-4-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



CL/EM: t_R= 1.32 min, 545.42 $(MH)^+$.

Ejemplo 76

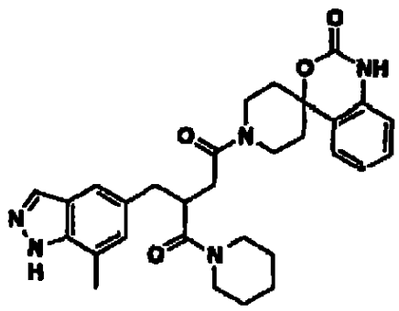
(±)-N,N-Dimetil-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxamida-4,4'-piperidinil]-butiramida



CL/EM: t_R = 1.27 min, 512.30 $(M+Na)^+$.

Ejemplo 77

(±)-2-(7-Metil-1H-indazol-5-ilmetil)-1-(piperidin-1-il)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxamida-4,4'-piperidinil]-butano-1,4-diona

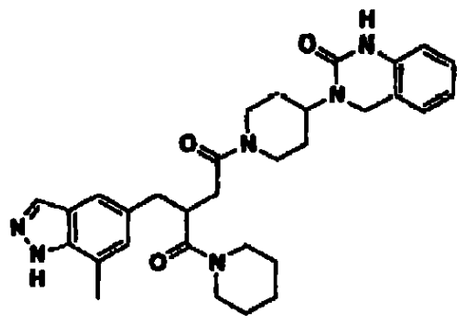


^{1}H-RMN (400 MHz, $CDCl_3$) δ 9.26-9.01 (1H, m), 8.09 (1H, s), 7.42-6.89 (7H, m), 4.56 (1H, m), 3.84 (1H, m), 3.65 (3H, m), 3.30 (2H, m), 3.05 (3H, m), 2.81 (1H, m), 2.60 (3H, s), 2.39 (1H, m), 2.09 (2H, m), 1.85 (1H, m), 1.43-0.79 (9H, m).

Espectro de masa: 530.34 $(MH)^+$.

Ejemplo 78

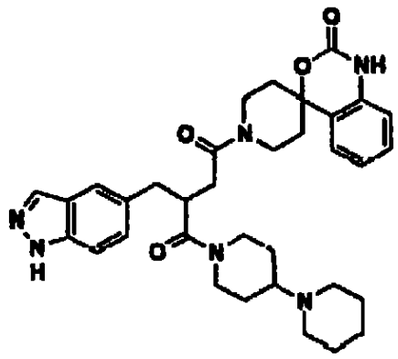
(±)-2-(7-Metil-1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-1-piperidin-1-il-butano-1,4-diona



^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.82 (1H, m), 7.37 (1H, m), 7.14 (1H, m), 7.04-6.90 (3H, m), 6.73 (1H, d, J = 8.0 Hz), 4.69 (1H, m), 4.56 (1H, m), 4.24 (2H, d, J = 7.2 Hz), 4.02 (1H, m), 3.65 (2H, m), 3.33 (3H, m), 3.07 (3H, m), 2.78 (1H, m), 2.55 (3H, s), 2.36 (1H, m), 1.80-1.50 (4H, m), 1.43 (4H, b), 1.26 (2H, b), 0.81 (2H, b). Espectro de masa: 543.40 $(MH)^+$.

Ejemplo 79

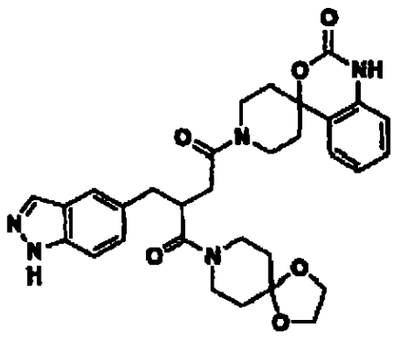
(±)-1-[1,4']Bipiperidinil-1'-il-2-(1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona



^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.86 (1H, m), 7.98 (1H, s), 7.54-6.85 (7H, m), 4.73-4.48 (3H, m), 3.96-.80 (3H, m), 3.73-3.58 (3H, m), 3.17-2.78 (5H, m), 2.55-2.24 (5H, m), 2.02-1.79 (6H, m), 1.70-0.79 (7H, m). Espectro de masa: 599.31 $(M+Na)^+$.

Ejemplo 80

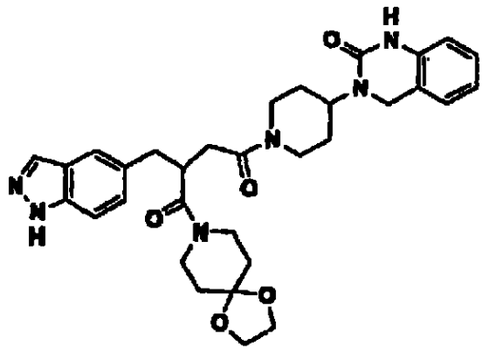
(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona



CL/EM: T_R = 1.25 min, 574.25 $(MH)^+$.

Ejemplo 81

(±)-1-(1,4-Dioxa-8-aza-espiro[4.5]dec-8-il)-2-(1H-indazol-5-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona

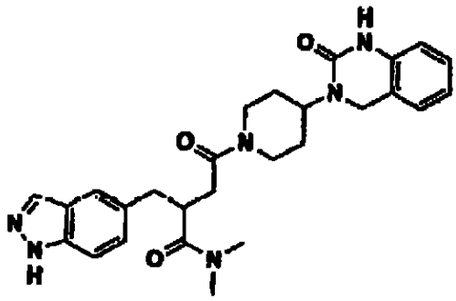


CL/EM: t_R= 1.34 min, 587.38 $(MH)^+$.

642

Ejemplo 82

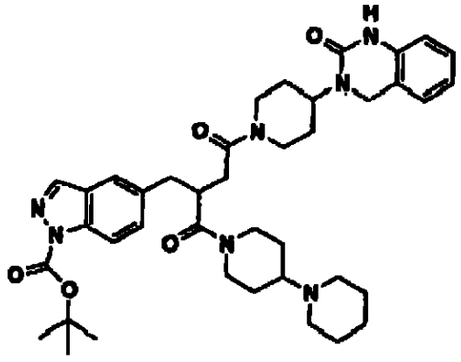
(±)-2-(1H-Indazol-5-ilmetil)-N,N-dimetil-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida



CL/EM: t_R = 1.28 min, 489.33 $(MH)^+$.

Ejemplo 83

Éster de tert-butilo del ácido (±)-5-{2-([1,4']bipiperidinil-1'-carbonil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butil}-indazol-1-carboxílico

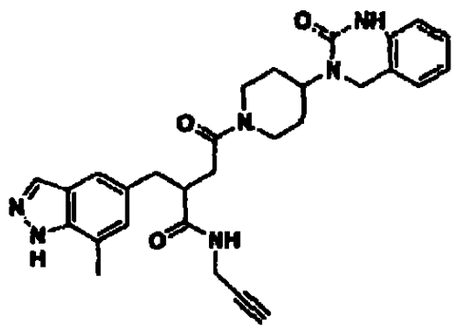


CL/EM: t_R = 1.47 min, 742.55 $(M+Na)^+$.

662 643

Ejemplo 84

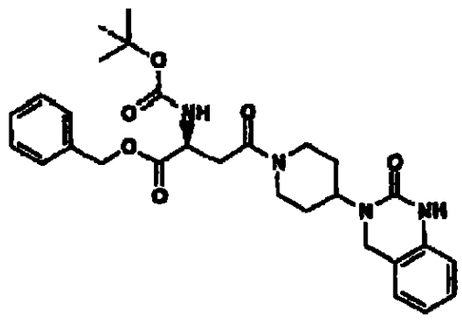
(±)-2-(7-Metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-N-prop-2-inil-butiramida



CL/EM: T_R = 33 min, 535.32 $(M+Na)^+$.

Intermediarios de aspartato y Ejemplos

Éster de bencilo del ácido (L)-2-tert-Butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

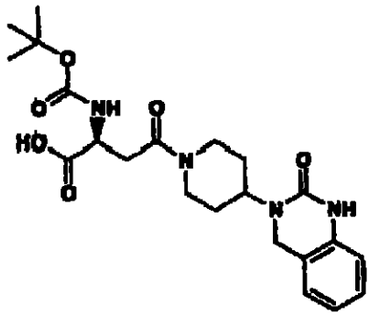


A una solución agitada de éster alfa-bencilo del ácido N-tert-butiloxicarbonil-L-aspártico (1.4 g, 4.33

667 644

mmol) y 3,4-dihidro-3-(4-piperidinil-2(1H)-quinazolinona (1.26 g, 4.33 mmol) en cloruro de metileno (12 mL) se le agregó 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 1.425 g, 4.76 mmol) en una porción seguido por adición gota a gota de trietilamina (0.724 mL, 5.20 mmol). La suspensión resultante gradualmente se volvió homogénea con agitación y se agitó a temperatura ambiente durante la noche (15 h). La mezcla se diluyó con cloruro de metileno y se lavó con hidróxido de sodio (0.5 N) y agua. Las capas se separaron y la capa orgánica se secó con sulfato de sodio, y se concentró in vacuo para dar una espuma amarilla ligera. El producto crudo se purificó por cromatografía de columna instantánea (metanol en cloruro de metileno al 10%) para dar un aceite incoloro. Espectro de masa: 559 $(M+Na)^+$.

ácido (L)-2-tert-Butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

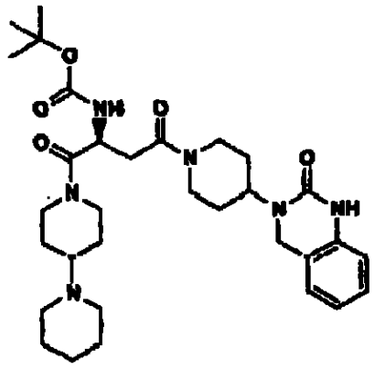


A una solución de éster de bencilo del ácido 2-tert-

butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico (1.48 g, 2.76 mmol) en acetato de etilo/metanol (16 mL, 1:1) en una botella Parr se le agregó carbón mineral peletizado al 10% (150 mg) en una porción. La hidrogenación se llevó a cabo con un aparato Parr a 52 psi (3.6556 Kg/cm^2) durante 1 h. CCD (metanol en cloruro de metileno al 10%) indicó una conversión cuantitativa. La mezcla se filtró y se concentró in vacuo para proporcionar un sólido incoloro vidrioso (1.14 g, 93%).

Ejemplo 85

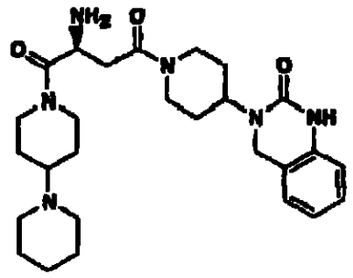
éster de tert-butilo del ácido (L)-{1-([1,4']Bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-carbámico



A una solución agitada de ácido 2-tert-butoxicarbonilamino-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico (1.14 g, 2.55 mmol) y 4-piperidinil-piperidina (525 mg, 2.81 mmol) en cloruro de metileno (20 mL) se le agregó 3-(dietoxifosforiloxi)1,2,3-

benzotriain-4(3H)-ona (DEPBT, 840 mg, 2.81 mmol) en una porción seguido por adición gota a gota de trietilamina (0.427 mL, 3.06 mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche (15 h). La mezcla se diluyó con cloruro de metileno y se lavó con solución de hidróxido de sodio (0.5 N) y agua. Las capas se separaron y la capa orgánica se secó con sulfato de sodio y se concentró in vacuo para dar una espuma amarilla ligera. El producto crudo se purificó por cromatografía de columna instantánea (10% (amoniaco en metanol 1M) en cloruro de metileno) para dar una espuma incolora (1.08 g, 71%). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.86-8.55 (1H, br), 7.05 (1H, br), 6.93 (1H, br), 6.82 (1H, br), 6.72 (1H, d, J = 7.6 Hz), 6.10-5.68 (1H, br), 5.20 (1H, m), 54.70-4.40 (2H, br), 4.20 (2H, br), 4.01-3.82 (2H, br.), 3.10-2.88 (3H, br), 2.99 (3H, br), 2.53 (6H, br), 1.90-1.10 (23H, m). Espectro de masa: 597 $(MH)^+$.

(L)-2-Amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona

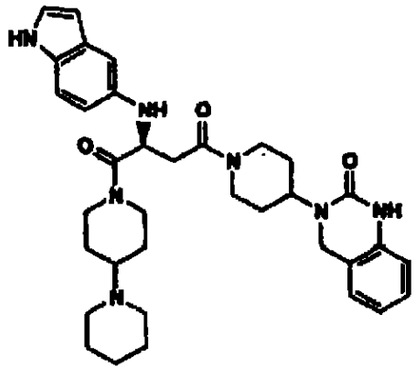


A una solución agitada de éster de tert-butilo del ácido

(1-([1,4']bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil)-carbámico (1.05 g, 1.76 mmol) en cloruro de metileno (12 mL) se le agregó ácido trifluroacético (2 mL). La mezcla se agitó a temperatura ambiente hasta completar la conversión (se monitoreó por CLEM, ca. 15 h). La mezcla se diluyó luego con agua e hidróxido de sodio (1.5 g) se le agregó lentamente con agitación. Las capas se separaron y la capa acuosa se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron sobre sulfato de sodio y se concentraron in vacuo para dar una espuma amarilla ligera (860 mg, 98%). Espectro de masa: 497 $(MH)^+$.

Ejemplo 86

(L)-1-[1,4']Bipiperidinil-1'-il-2-(1H-indol-5-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



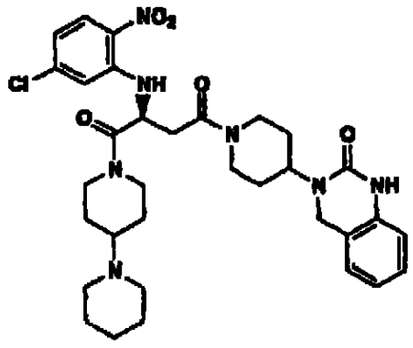
A una solución de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-

butano-1,4-diona (52 mg, 0.105 mmol) y N-tert-BOC-5-bromo-indol (se preparó como se describe en Tetrahedron 2000, pp 8473-8482) (31 mg, 0.105 mmol) en tetrahidrofurano (1 mL) en un vial de cilindro 5 mL se le agregó 2-diciclohexilfosfino-2'-(N,N-dimetilamino)-bifenil (4.1 mg, 0.0105 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.005 mmol), y carbonato de cesio (54.6 mg, 0.168 mmol) bajo nitrógeno. El vial se selló con un tapón de línea de teflon®. La mezcla de reacción color anaranjado oscuro se calentó a 80°C con agitación. La reacción se continuó a 80°C durante la noche. La conversión alcanzó aproximadamente 50% después de 17 h. El solvente se removió in vacuo y el residuo se disolvió en cloruro de metileno y se filtró. El producto deseado se purificó por CCD preparativa (metanol en cloruro de metileno 10%) para proporcionar el producto protegido por tert-butiloxicarbonilo (11 mg, 15%). Espectro de masa: 712 $(MH)^+$. Este intermediario (11 mg) se disolvió en cloruro de metileno 3 mL y se trató con ácido trifluoroacético (1.5 mL). La solución incolora se volvió a un color canela y se agitó a temperatura ambiente durante 1.5 h. La mezcla se concentró in vacuo y se secó bajo alto vacío para dar un polvo color canela (15 mg, 100%). Espectro de masa: 612 $(MH)^+$.

649

Ejemplo 87

(L)-1-[1,4']Bipiperidinil-1'-il-2-(5-cloro-2-nitro-fenilamino)-4-[4-(2-oxo-1,4-4-diona

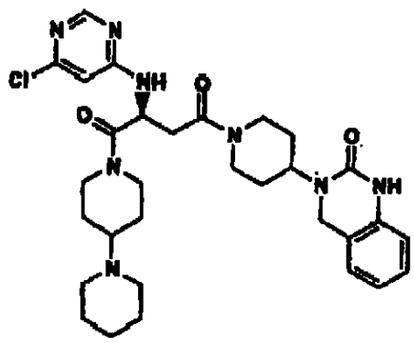


A una solución agitada 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (33.7 mg, 0.068 mmol) y 4-cloro-1,2-dinitrobenceno (16.8 mg, 0.075 mmol) en etanol (0.5 mL) se le agregó una solución de bicarbonato de sodio saturada (4 gotas). La mezcla se agitó a temperatura ambiente durante 70 h hasta aproximadamente el 60% de conversión. El producto se purificó por CLAR preparativa para dar un sólido amarillo (17.7 mg, 40%). Espectro de masa: 652 $(MH)^+$.

650 650

Ejemplo 88

(L)-1-[1,4']Bipiperidinil-1'-il-2-(6-cloro-pirimidin-4-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



Una mezcla de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (22.3 mg, 0.045 mmol) y 4,6-dicloropirimidina (16 mg, 0.095 mmol) en 2-propanol (0.5 mL) en un vial procesable por microondas se calentó a 130°C bajo irradiación de microondas durante 40 min. CL/EM indicó 90% de conversión. El solvente se removió in vacuo y el residuo se dividió entre cloruro de metileno y solución de hidróxido de sodio 1 N. La capa orgánica se separó, se secó sobre sulfato de sodio, y se concentró in vacuo. El residuo se purificó por cromatografía de columna instantánea (10% (amoniaco en metanol 1N) en cloruro de metileno) para proporcionar un sólido blanco (23 mg, 84%). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 12.8 Hz), 8.04-7.81 (1H, 2s), 7.14 (1H, t, J = 7.6 Hz), 7.10-6.80 (2H, m), 6.74 (1H, t, J = 8.2 Hz), 6.52-6.42 (1H, m), 5.90-5.50 (1H, br), 4.85-4.40 (3H, m), 4.40-4.05 (3H, m), 4.05-3.82 (1H, m), 3.20-3.00 (2H, m), 3.00-2.68 (2H, m), 2.68-2.30 (8H, m), 2.05-1.90 (2H,

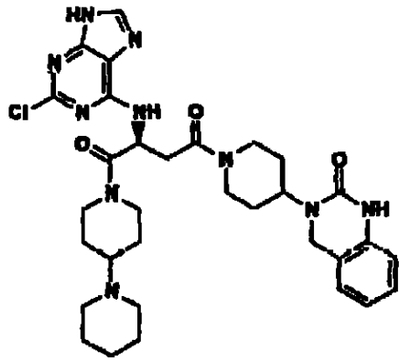
671 651

m), 1.90-0.70 (12H, m). Espectro de masa: 609 $(MH)^+$.

Preparado similarmente:

Ejemplo 89

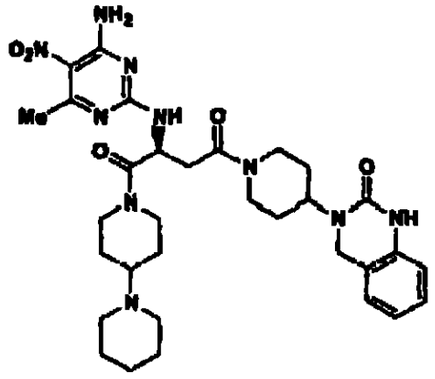
(L)-1-[1,4']Bipiperidinil-1'-il-2-(2-cloro-9H-purin-6-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



CL/EM: t_R = 1.10 min, 649 $(MH)^+$.

Ejemplo 90

(L)-2-(4-Amino-6-metil-5-nitro-pirimidin-2-ilamino)-1-[1,4']bipiperidinil-1'-il-4-[4-(2-cloro-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona

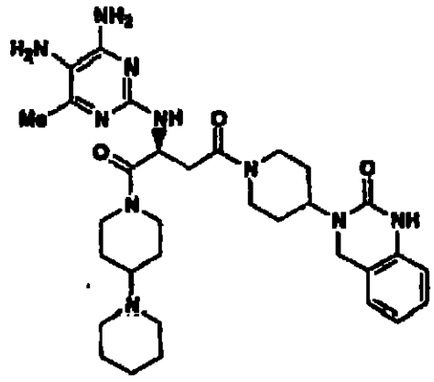


CL/EM: t_R = 1.12 min, 649 $(MH)^+$.

GT 652

Ejemplo 91

(L)-1-[1,4']Bipiperidinil-1'-il-2-(4,5-diamino-6-metil-pirimidin-2-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



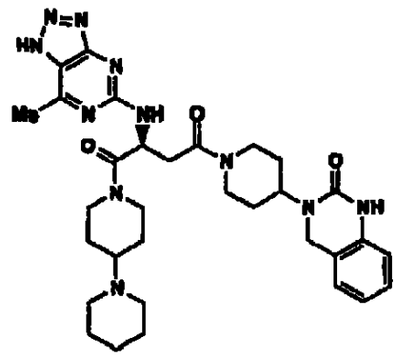
A una solución de 2-(4-amino-6-metil-5-nitro-pirimidin-2-ilamino)-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona en 2:1 metanol/acetato de etilo (6 mL) en una botella Parr se le agregó carbón mineral peletizado 10% (60 mg). La mezcla se agitó bajo una atmósfera de hidrógeno a 55 psi (3.8665 Kg/cm^2) durante 20 h. La mezcla se filtró a través de celite y el filtrado se concentró in vacuo para proporcionar un sólido incoloro (41.2 mg, 49.2% durante dos etapas).

CL/EM: t_R = 0.86 min, 619 $(MH)^+$.

BTC 653

Ejemplo 92

(L)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-[1,2,3]triazolo[4,5-d]pirimidin-5-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



A una solución agitada de 1-[1,4']bipiperidinil-1'-il-2-(4,5-diamino-6-metil-pirimidin-2-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (10.6 mg, 0.0125 mmol) en ácido acético (1.5 mL) se le agregó nitrito de sodio (24 mg) seguido por algunas gotas de agua. La solución amarilla ligera resultante se agitó a temperatura ambiente durante 6 h. La mezcla de reacción se diluyó con agua y metanol y se purificó por CLAR preparativa para proporcionar un aceite/sólido incoloro (3.0 mg, 28%). CL/EM: T_R = 1.07 min, 630 $(MH)^+$.

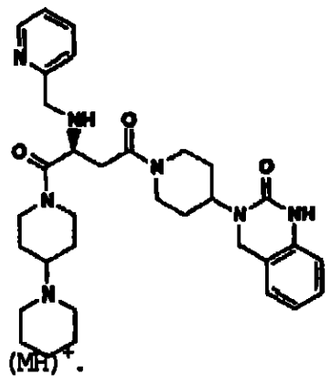
Procedimiento general para las síntesis de los Ejemplos 93-95:

Una mezcla de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (0.014 mmol), uno de unas series de aldehídos (0.07 mmol, 5 equiv) y sulfato de magnesio anhidro sólido (0.031 mmol, 2.2 equiv) en 1,2-dicloroetano (3.0 mL) se trató con una cantidad catalítica de ácido acético y se

agitó durante la noche. El cianoborohidruro de sodio (0.07 mmol, 5 eq) se agregó luego en una porción y la suspensión se agitó nuevamente durante la noche. La purificación se llevó a cabo ya sea por filtración a través un cartucho SCX o por CLAR preparativa.

Ejemplo 93

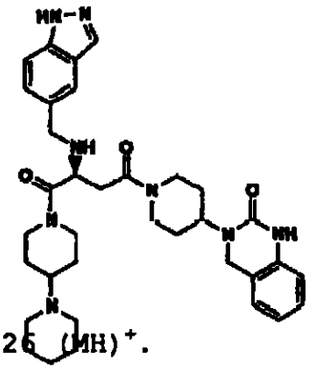
(L)-1-[1,4']Bipiperidinil-1'-il-2-((2'-piridil)-metil-amino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



CL/EM: T_R = 0.87 min, 588 $(MH)^+$.

Ejemplo 94

(L)-1-[1,4']Bipiperidinil-1'-il-2-((5'-indazolil)-metil-amino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona

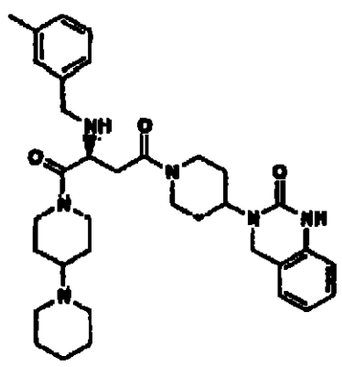


CL/EM: t_R = 0.92 min, 626 $(MH)^+$.

674 655

Ejemplo 95

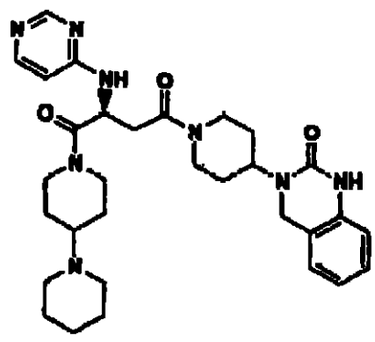
(L)-1-[1,4']Bipiperidinil-1'-il-2-((3'-metil-fenil))-metil-amino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



CL/EM: t_R = 1.08 min, 600 $(MH)^+$.

Ejemplo 96

(L)-1-[1,4']Bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-2-(pirimidin-4-ilamino)-butano-1,4-diona



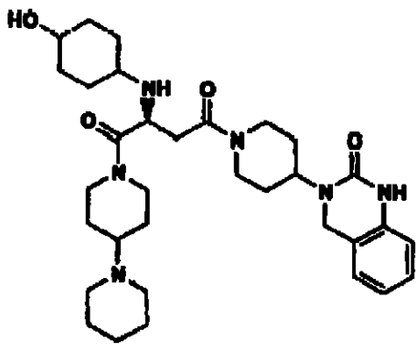
A una solución de 1-[1,4']bipiperidinil-1'-il-2-(6-cloro-pirimidin-4-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (21 mg) se disolvió en acetato de etilo/metanol 4 mL (1:1)

675 656

en una botella Parr se agregó carbón mineral peletizado 10% (10 mg). La hidrogenación se llevó a cabo en un aparato Parr a 55 psi (3.8665 Kg/cm^2) durante la noche. La mezcla desgasificada se filtró luego y se concentró in vacuo. El residuo se purificó por CLAR preparativa para proporcionar un sólido amarillo (12.4 mg, 45%). Espectro de masa: 575 $(MH)^+$.

Ejemplo 97

(L)-1-[1,4']Bipiperidinil-1'-il-2-[4-hidroxi-ciclohexilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



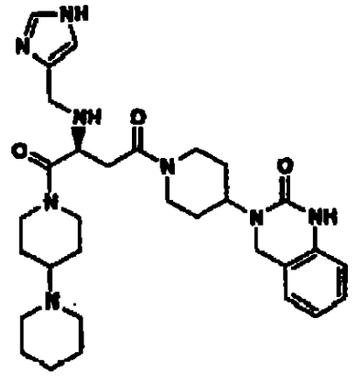
A una mezcla agitada de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (47.9 mg, 0.096 mmol) y 4-hidroxi-ciclohexanona (Síntesis reportada en Can. J. Chem. 1994, 72, 1699-1704) (11 mg, 0.096 mmol) en metanol (1.0 mL) se le agregó cloruro de zinc en exceso seguido por cianoborohidruro de sodio (5 equiv). La suspensión se agitó a temperatura

675 657

ambiente durante 6 días. El metanol se removió in vacuo y el residuo se dividió entre cloruro de metileno y hidróxido de sodio 1 N. La capa acuosa se extrajo con cloruro de metileno (3x). La solución de cloruro de metileno combinado se pasó a través de un cartucho de celite y se concentró in vacuo. El residuo se purificó por CCD preparativa (10% (amoniaco en metanol 1N) en cloruro de metileno) para proporcionar el producto deseado como un sólido blanco (15.3 mg, 27%). Espectro de masa: 595 $(MH)^+$.

Ejemplo 98

(L)-1-[1,4']Bipiperidinil-1'-il-2-[(1H-imidazol-4-ilmetil)-amino]-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



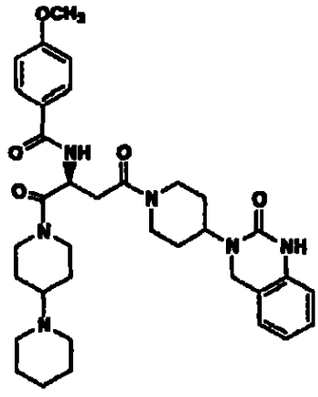
A una solución agitada de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (20.6 mg, 0.0415 mmol) y 4-imidazolcarboxialdehído (4 mg, 0.0415 cloruro de metileno (1.0 mL) se le agregó cianoborohidruro de sodio (8.8 mg, 0.0415 mmol) en una porción. La suspensión se agitó a

677 658

temperatura ambiente durante 2 días y luego se dividió entre cloruro de metileno e hidróxido de sodio 1N. Las capas se separaron y la capa acuosa se extrajo con cloruro de metileno. Las capas orgánicas combinadas se secaron sobre sulfato de sodio, y se concentraron in vacuo. El residuo se purificó por CCD preparativa (10% (amoniaco en metanol 1N) en cloruro de metileno) para proporcionar el producto deseado como un aceite incoloro que se solidificó durante el reposo (6.1 mg, 26%). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 7.61 (1H, d, J = 4.8 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.10-6.85 (3H, m), 6.67 (1H, d, J = 8.0 Hz), 4.85-4.63 (2H, m), 4.63-4.40 (1H, m), 4.40-3.65 (7H, m), 3.25-2.40 (10H, m), 2.15-0.70 (18H, m). Espectro de masa: 577 $(MH)^+$.

Ejemplo 99

(L)-N-{1-([1,4']Bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-4-metoxi-benzamida



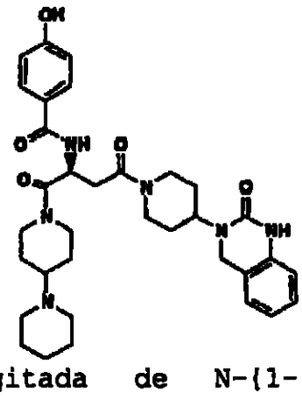
A una mezcla agitada de 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-

GPT 659

1,4-diona (91.5 mg, 0.184 mmol) y cloruro p-anisoilo (34.6 mg, 0.203 mmol) en cloruro de metileno se agregó dos gotas de trietilamina (35 µL). La solución amarilla ligera se agitó a temperatura ambiente durante 2.5 h para realizar la conversión completa. La mezcla de reacción se lavó con hidróxido de sodio (1N) y la capa acuosa se extrajo luego con cloruro de metileno. Las capas orgánicas combinadas se pasaron a través de un cartucho de celite y se concentraron in vacuo para dar un sólido vidrioso. El producto crudo se purificó por cromatografía de columna instantánea (10% (amoniaco en metanol 1N) en cloruro de metileno) para dar un sólido vidrioso (92.8 mg, 80%). ^{1}H-RMN (400 MHz, $CDCl_3$) δ 8.55-8.47 (1H, d), 8.10-7.78 (3H, m), 7.09 (1H, t, J = 7.4 Hz), 6.96-6.74 (4H, m), 5.62-5.44 (1H, br), 4.75-4.40 (3H, m), 4.40-4.05 (3H, m), 4.05-3.82 (1H, br), 3.76 (3H, s), 3.18-2.88 (3H, m), 2.88-2.70 (1H, m), 2.70-2.30 (8H, m), 2.05-1.19 (14H, m). Espectro de masa: 631 $(MH)^+$.

Ejemplo 100

(L)-N-{1-([1,4']Bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-4-metoxi-benzamida

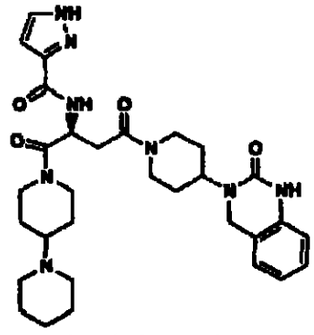


Una solución agitada de N-{1-([1,4]bipiperidinil-1'-

carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil)-4-metoxi-benzamida solución en cloruro de metileno (69 mg) se trató con tribromuro de boro (en cloruro de metileno 1M, 0.6 mL), gota a gota a temperatura ambiente. La suspensión resultante se agitó a temperatura ambiente durante 7 h y luego la reacción se apagó con trietilamina en exceso seguido por metanol. Los solventes se removieron in vacuo y el residuo se disolvió en metanol y se purificó por CLAR preparativa. CL/EM: T_R = 1.03 min, 617 $(MH)^+$.

Ejemplo 101

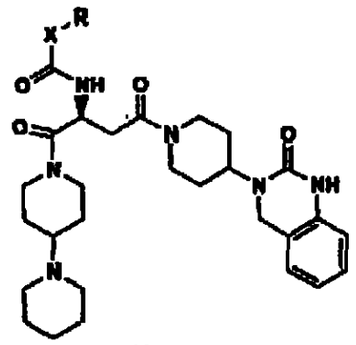
{1-([1,4']Bipiperidinil-1'-carbonil)-3-oxo-3-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-propil}-amida del ácido (L)-1H-pirazol-3-carboxilico



A una solución agitada de ácido pirrazol-3-carboxílico (4 mg, 0.036 mmol) y 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona (13 mg, 0.026 mmol) en cloruro de metileno mL) se le agregó 3-(dietoxifosforiloxi)-1,2,3-benzotriain-4(3H)-ona (DEPBT, 8.6 mg, 0.036 mmol) en una porción seguido por una gota de trietilamina. La mezcla resultante se agitó a temperatura ambiente durante la noche (15 h). La mezcla se

dividió luego entre hidróxido de sodio (0.5 N) y cloruro de metileno. Las capas se separaron y la capa acuosa se extrajo con cloruro de metileno (3x). CLEM indicó que el producto se mantiene en la capa acuosa. El producto se purificó por CLAR preparativa para dar un aceite amarillo (17.2 mg, 94%). Espectro de masa: 591 $(MH)^+$.

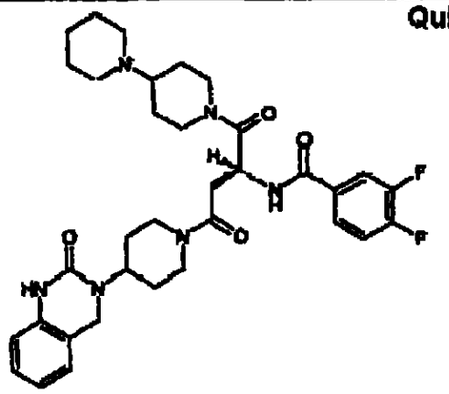
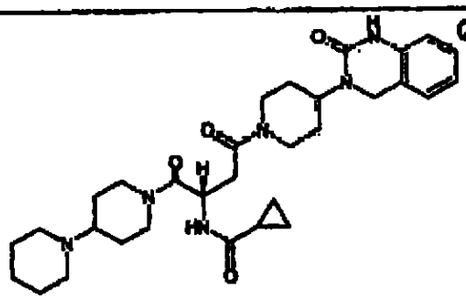
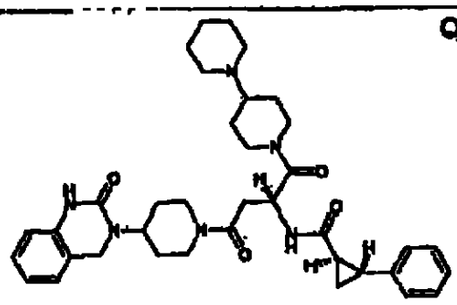
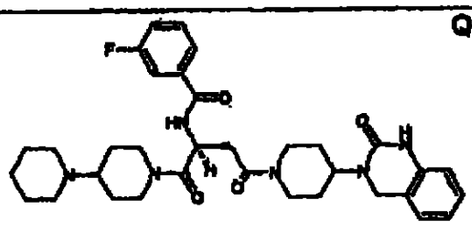
Procedimiento general para las síntesis de los Ejemplos 102-134:

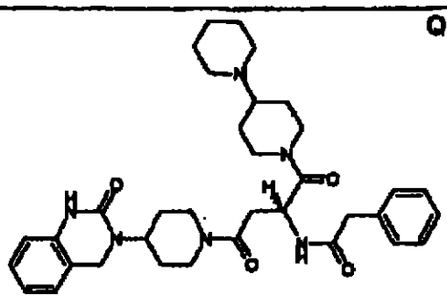
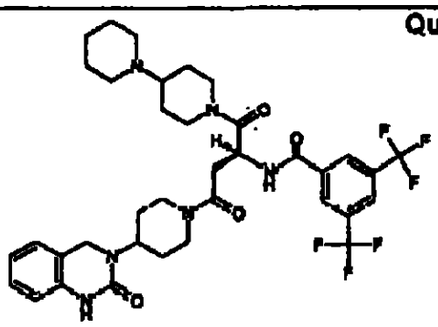
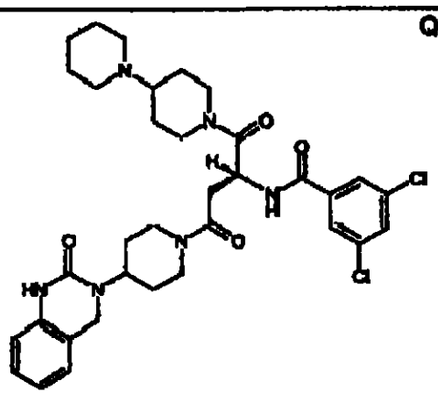
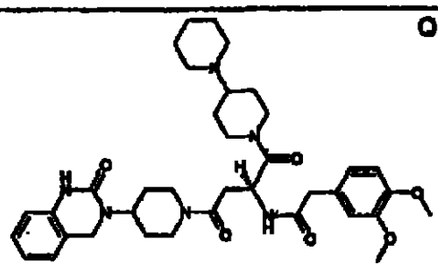


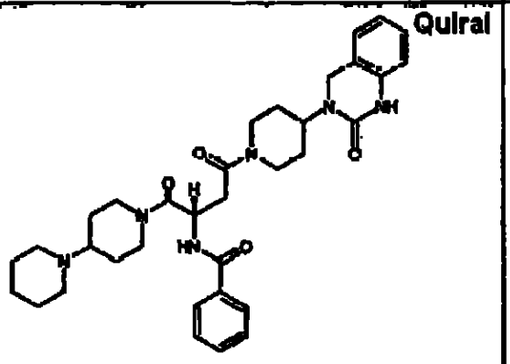
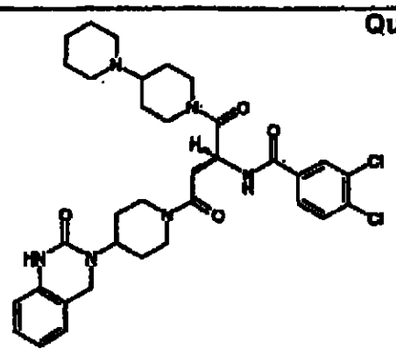
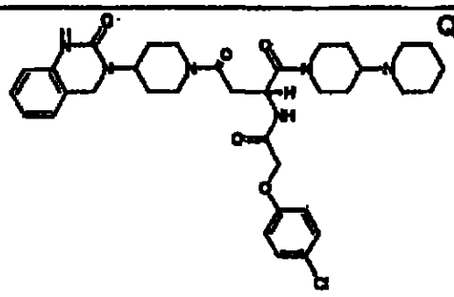
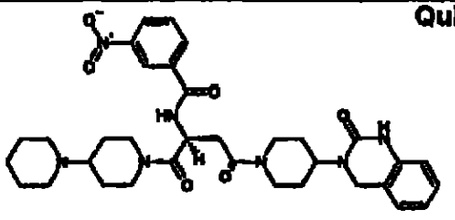
X = C, O

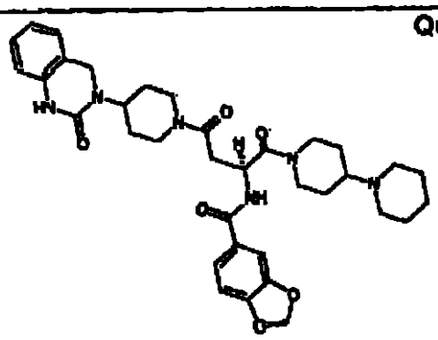
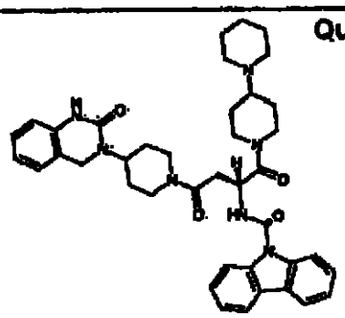
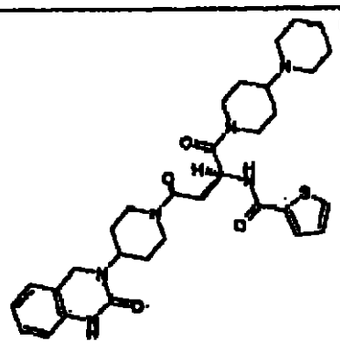
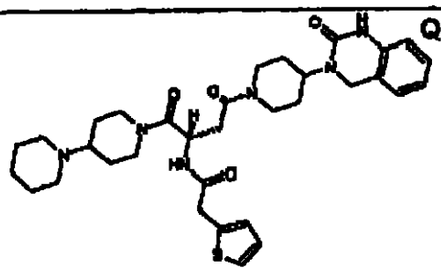
La amina de partida, 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona, se dispersó en un mini-reactor de 96 pozos (ca. 10 mg cada uno) en dicloroetano 1 mL. Cloruros acilo individuales (ca. 2 equiv.) se agregaron seguido por una base de piperidina de fase sólido enlazada a la resina (4 equiv). El bloque se agitó durante la noche. Aproximadamente 4 equivalentes de resina tris-amina se agregó a cada pozo y el mini-reactor se agitó durante otras 5 h. Las mezclas de reacción se filtraron, y purificaron por ya sea CLAR preparativa o por filtración a través un cartucho SCX o por ambos. Los tiempos de retención CLAR y datos de espectro de masa para cada ejemplo se enlistan en la Tabla 2.

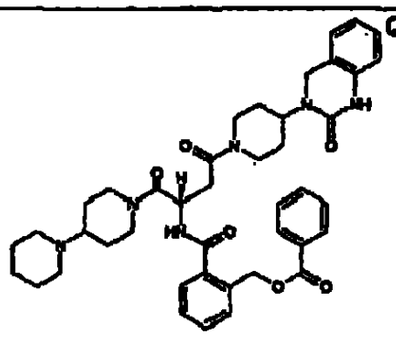
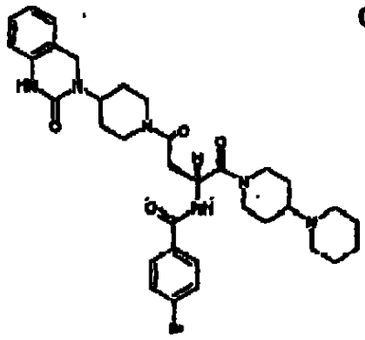
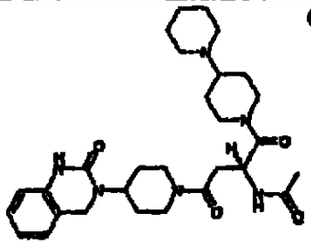
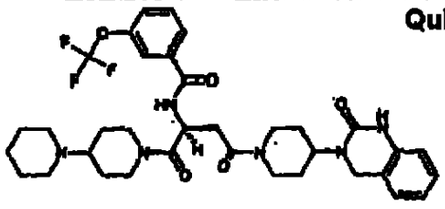
Tabla 2. Amidas y Carbamatos

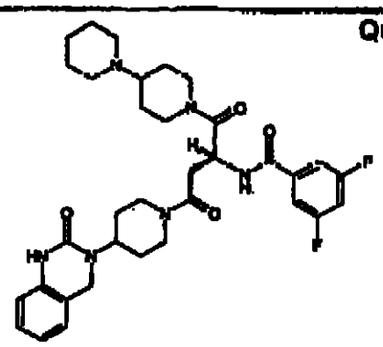
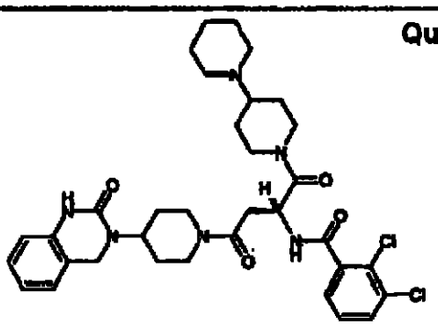
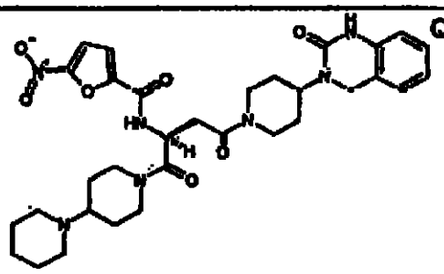
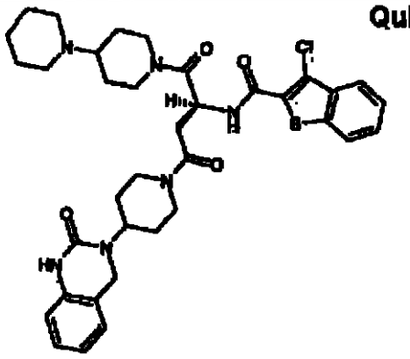
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
102	Quiral 	1.84	637.38
103	Quiral 	1.39	565.45
104	Quiral 	1.89	641.46
105	Quiral 	1.73	619.42

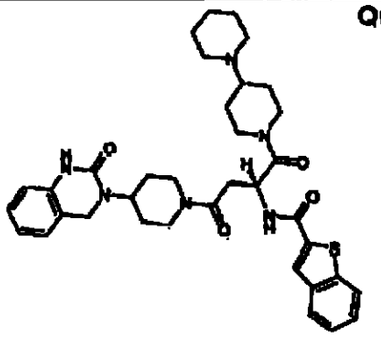
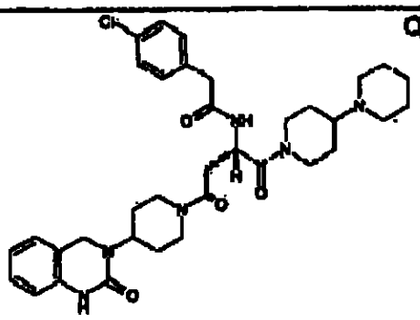
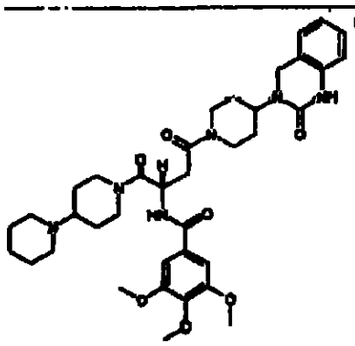
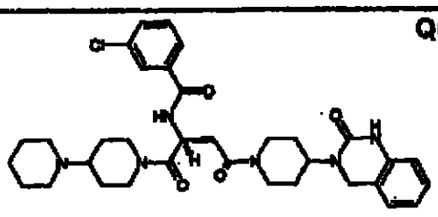
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
106	Quiral 	1.62	615.41
107	Quiral 	2.25	737.37
108	Quiral 	2.12	669.3
109	Quiral 	1.59	675.46

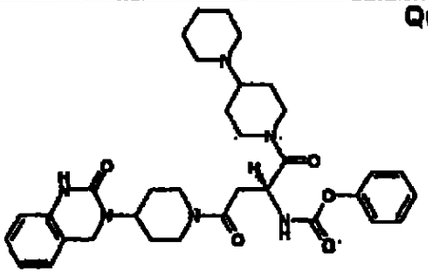
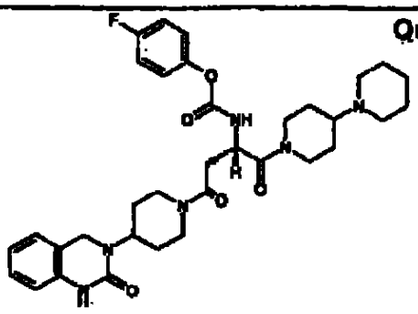
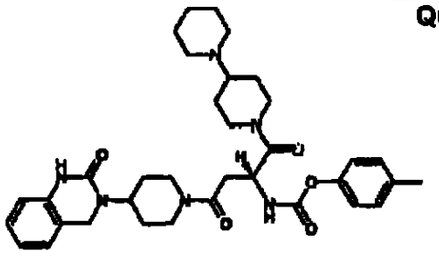
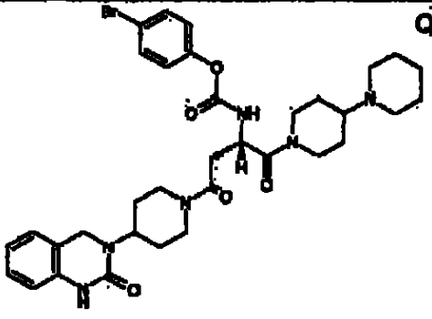
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
110	 Quiral	1.62	601.43
111	 Quiral	2.09	669.33
112	 Quiral	1.91	665.36
113	 Quiral	1.68	646.37

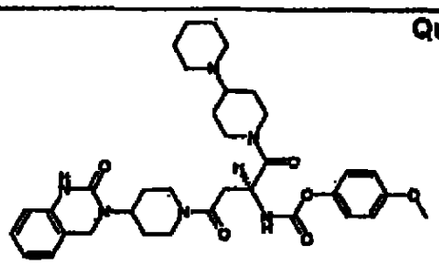
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
114	Quiral 	1.66	645.4
115	Quiral 	2.14	690.45
116	Quiral 	1.59	607.39
117	Quiral 	1.59	621.4

Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
118	Quiral 	2.01	735.43
119	Quiral 	1.92	679.32
120	Quiral 	1.22	537.4
121	Quiral 	2.03	685.4

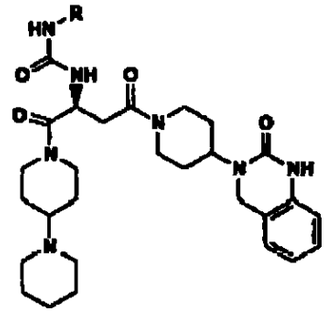
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
122	Quiral 	1.79	637.38
123	Quiral 	1.84	669.3
124	Quiral 	1.53	636.35
125	Quiral 	2.04	691.35

Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
126	Quiral 	1.89	657.35
127	Quiral 	1.86	649.39
128	Quiral 	1.67	691.42
129	Quiral 	1.84	635.38

Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
130	Quiral 	1.69	617.42
131	Quiral 	1.74	635.38
132	Quiral 	1.84	631.44
133	Quiral 	1.94	695.28

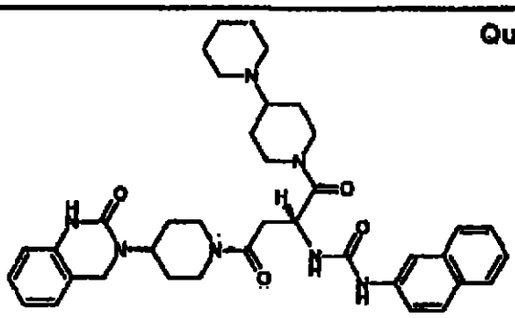
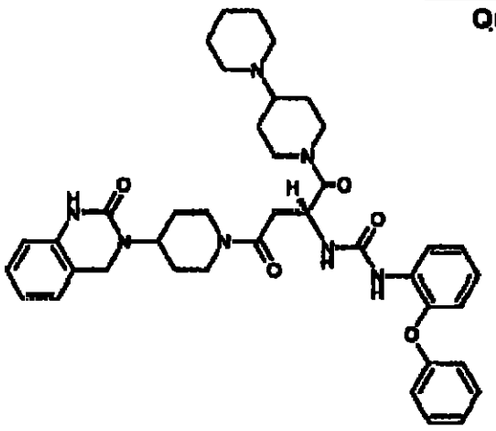
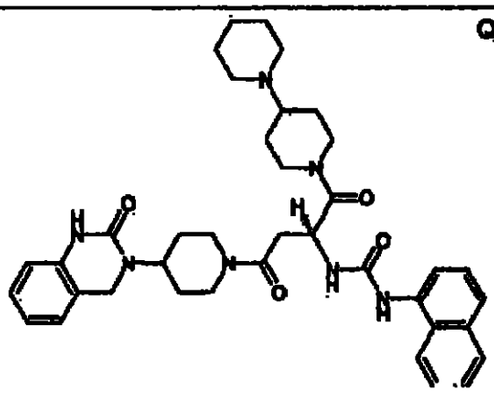
Ejemplo	Estructura	CLAR t_R (min)	EM (M+)
134	Quiral 	1.7	647.41

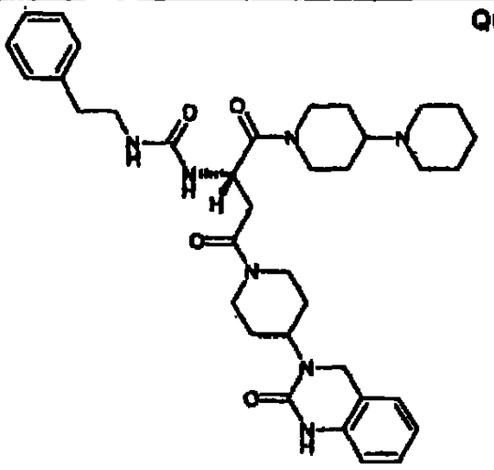
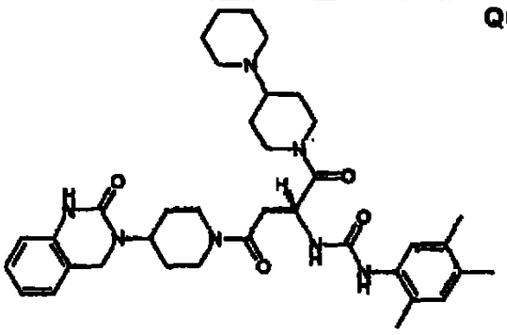
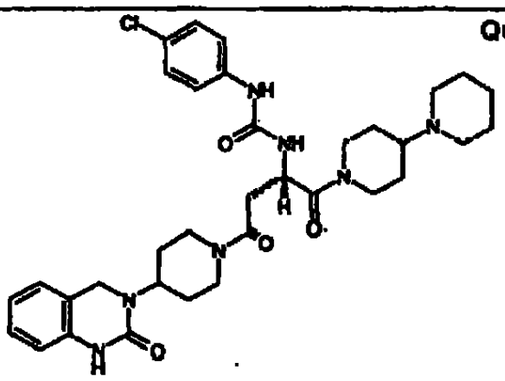
Procedimiento general para las síntesis de los Ejemplos 135-200:



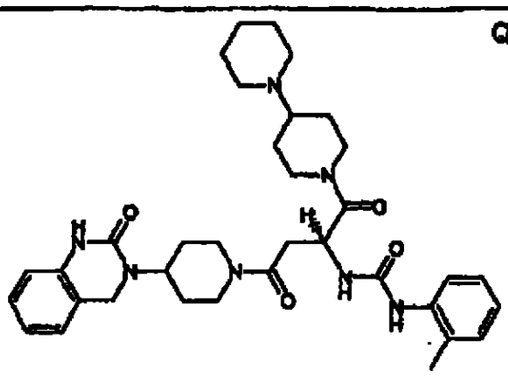
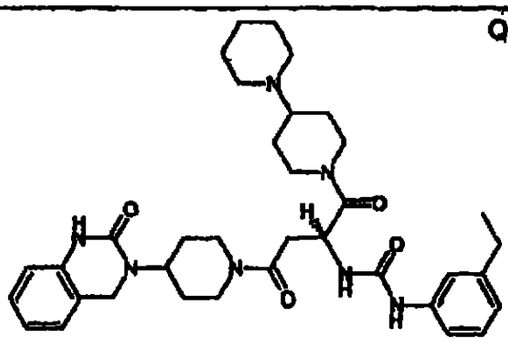
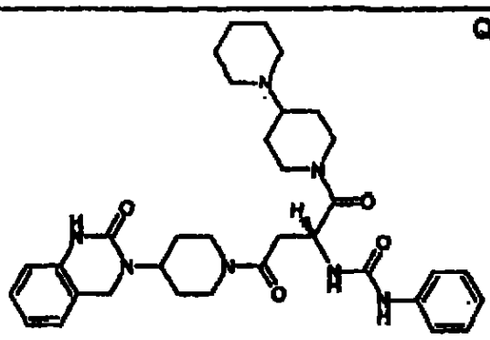
La amina de partida, 2-amino-1-[1,4']bipiperidinil-1'-il-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona, se dispersó en un mini-reactor de 96 pozos (ca. 10 mg en cada pozo) en dicloroetano (1 mL). Isocianatos individuales (ca. 2 equiv) se agregaron a pozos individuales. El bloque se agitó durante 2 días. Aproximadamente 4 equivalentes de resina tris-amina se agregó a cada pozo y el mini-reactor se agitó durante otros dos días. Las mezclas de reacción se filtraron, y el producto individual se purificó por ya sea CLAR preparativa o filtración a través de un cartucho SCX o ambos. Tiempos de retención CLAR y datos de espectro de masa para cada ejemplo se enlistan en la Tabla 3.

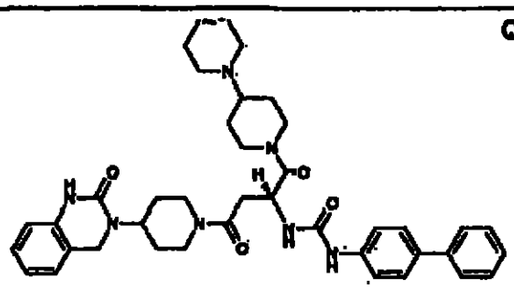
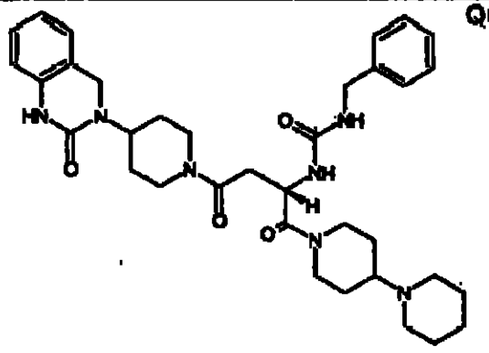
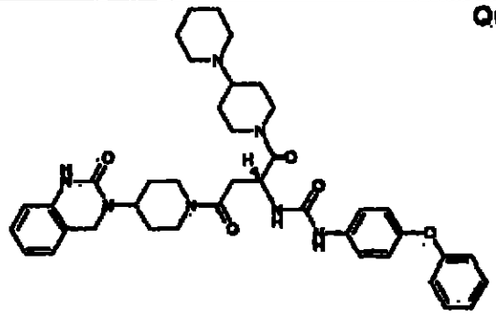
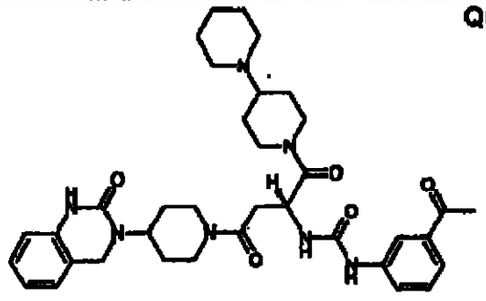
Tabla 3. Ureas

Ejemplo	Estructura	CLAR C_{TR} (min)	EM $(MH)^+$
135	Quiral 	1.43	665.84
136	Quiral 	1.56	707.88
137	Quiral 	1.39	665.84

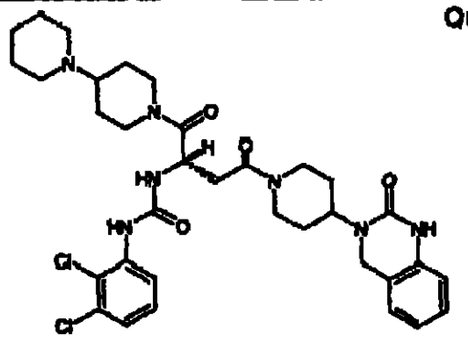
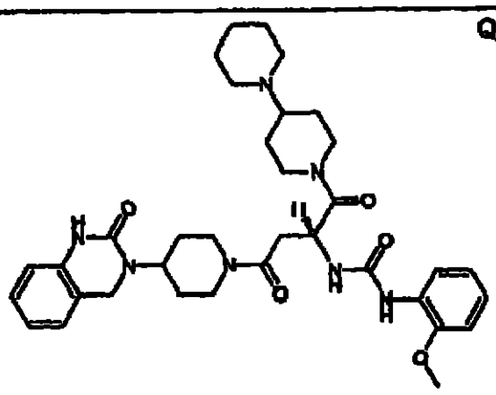
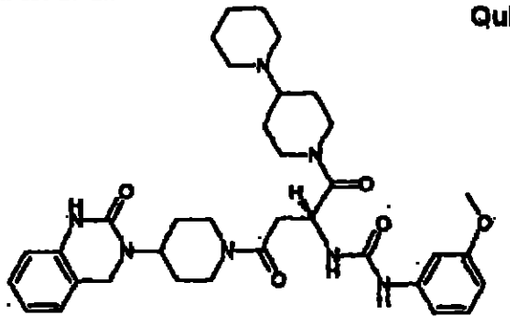
Ejemplo	Estructura	CLAR: C t_R (min)	EM $(MH)^+$
138	Quiral 	1.3	643.83
139	Quiral 	1.44	657.86
140	Quiral 	1.42	650.22

694 673

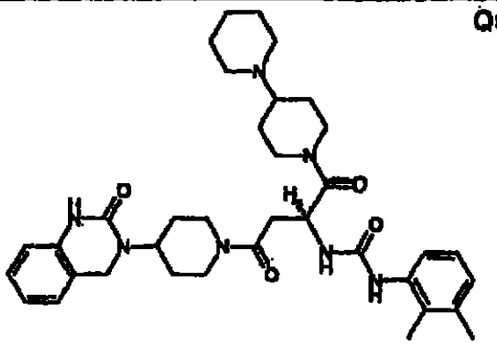
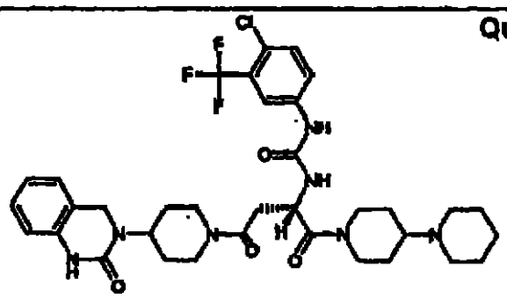
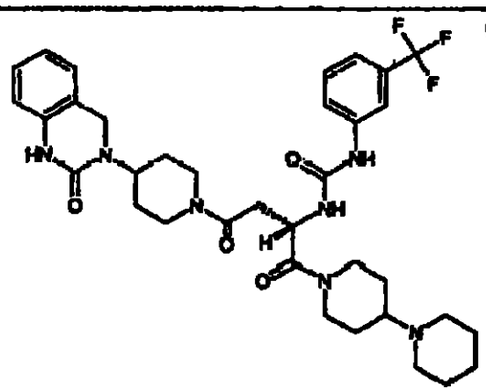
Ejemplo	Estructura	CLAR C t_R (min)	EM $(MH)^+$
141	Quiral 	1.26	629.81
142	Quiral 	1.41	643.83
143	Quiral 	1.24	615.78

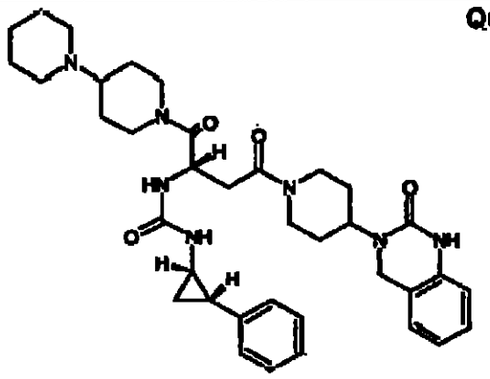
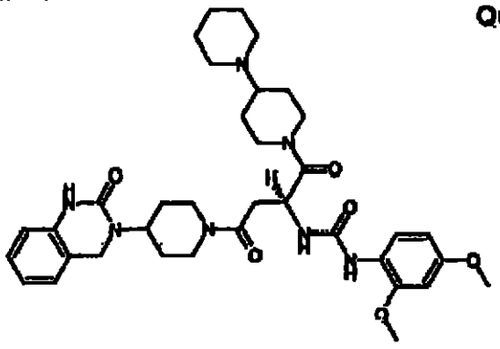
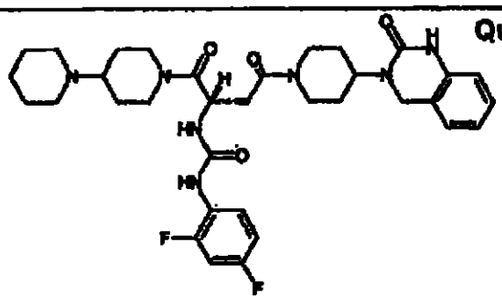
Ejemplo	Estructura	CLAR C_{tr} (min)	EM $(MH)^+$
144	Quiral 	1.53	691.88
145	Quiral 	1.21	629.81
146	Quiral 	1.52	707.88
147	Quiral 	1.19	657.82

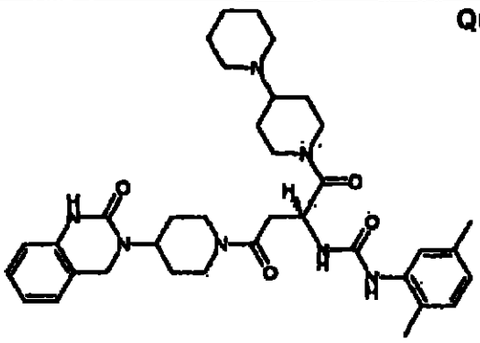
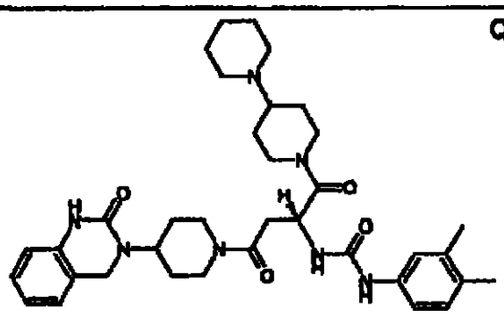
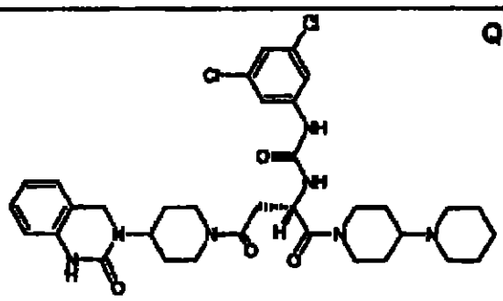
697 675

Ejemplo	Estructura	CLAR t_R (min)	EM $(MH)^+$
148	Quiral 	1.44	684.67
149	Quiral 	1.3	645.81
150	Quiral 	1.24	645.81

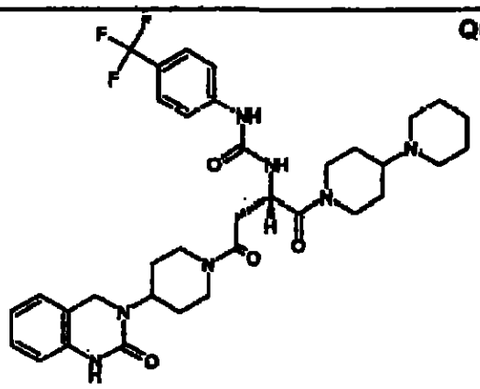
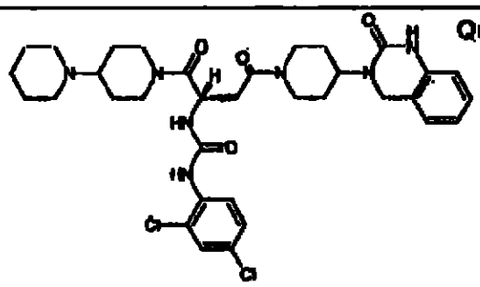
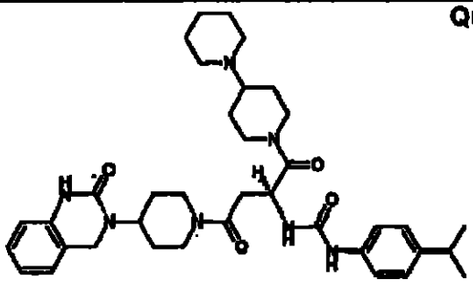
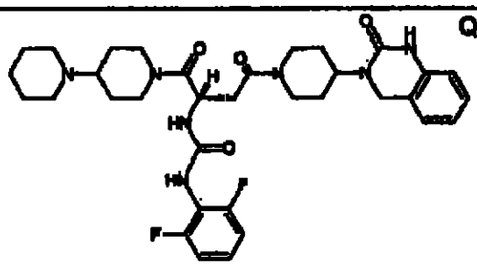
694 676

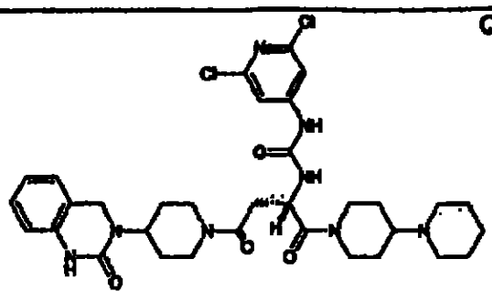
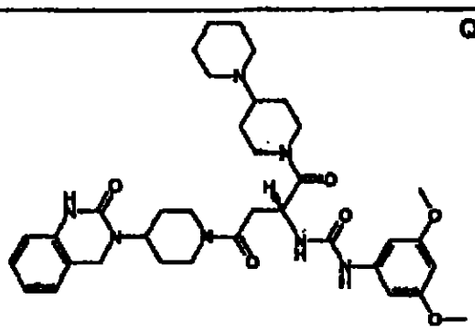
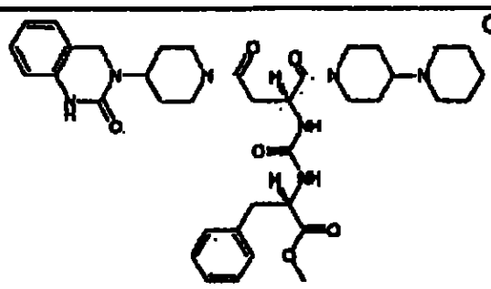
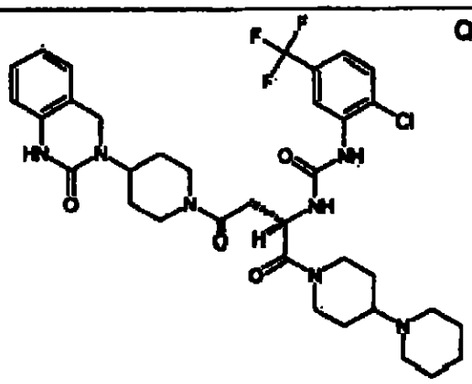
Ejemplo	Estructura	CLAR t_R (min)	EM $(MH)^+$
151	Quiral 	1.33	643.83
152	Quiral 	1.56	718.22
153	Quiral 	1.55	683.78

Ejemplo	Estructura	CLAR C_{f_R} (min)	EM $(MH)^+$
154	Quiral 	1.37	655.84
155	Quiral 	1.27	675.83
156	Quiral 	1.26	651.76

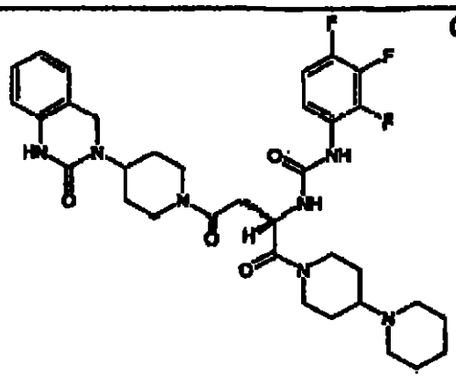
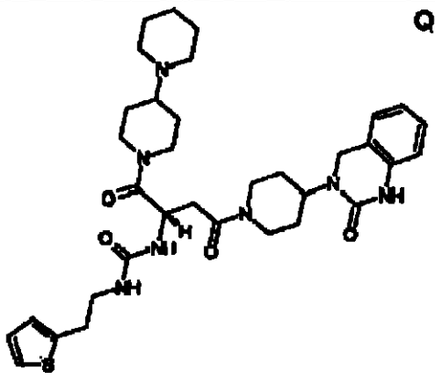
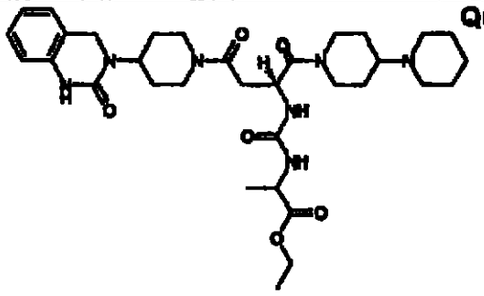
Ejemplo	Estructura	CLAR C_{18} (min)	EM $(MH)^+$
157	Quiral 	1.39	643.83
158	Quiral 	1.43	643.83
159	Quiral 	1.57	684.67

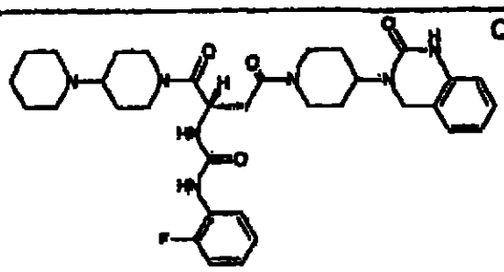
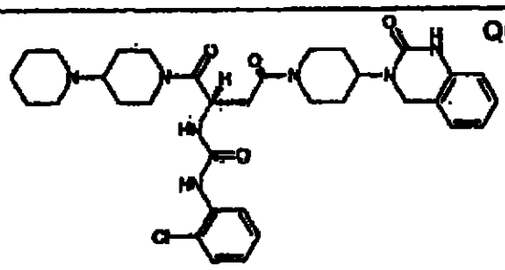
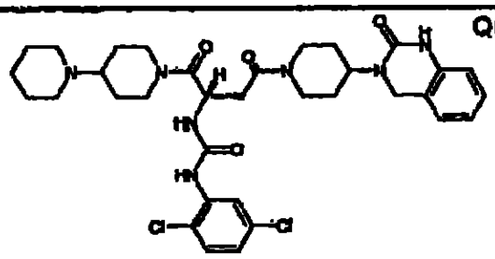
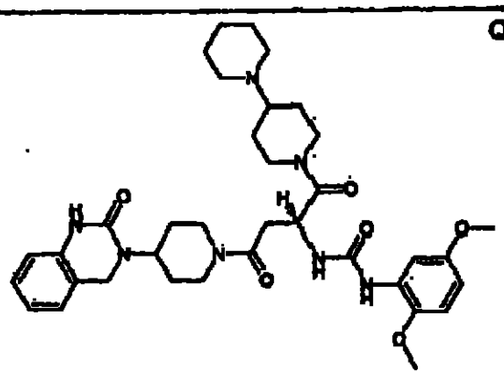
707 679

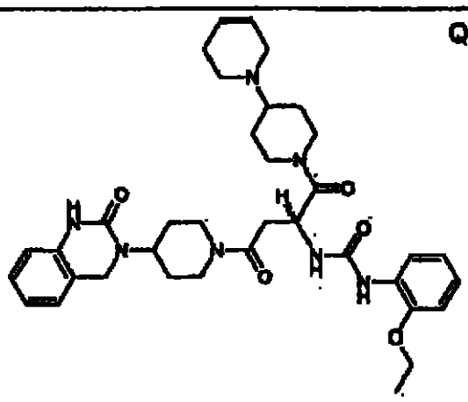
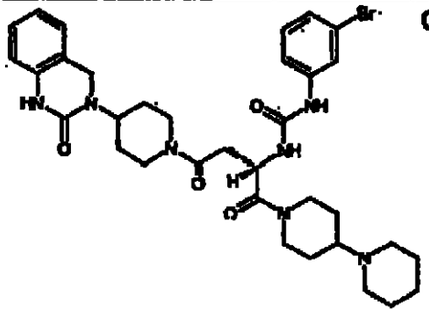
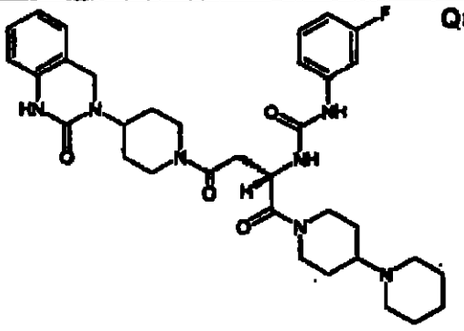
Ejemplo	Estructura	HPLC t_R (min)	MS. $(MH)^+$
160	Quiral 	1.46	683.78
161	Quiral 	1.48	684.67
162	Quiral 	1.5	657.86
163	Quiral 	1.14	651.76

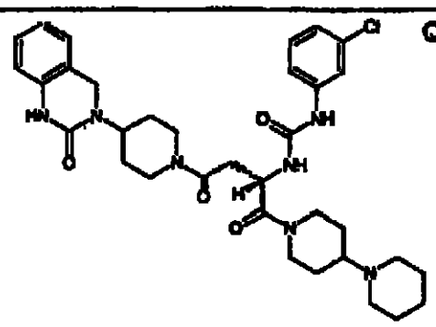
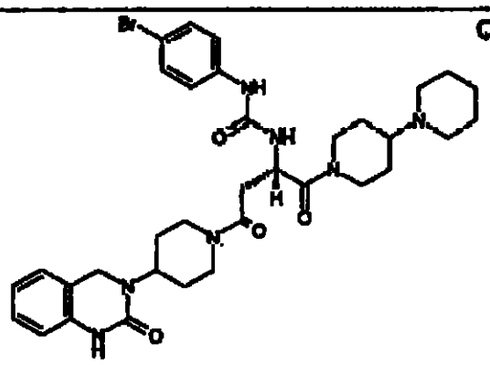
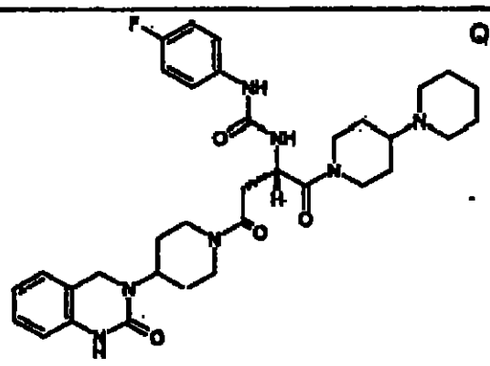
Ejemplo	Estructura	CLAR C tR (min)	EM (MH)+
164	Quiral 	1.34	685.66
165	Quiral 	1.26	675.83
166	Quiral 	1.28	701.87
167	Quiral 	1.52	718.22

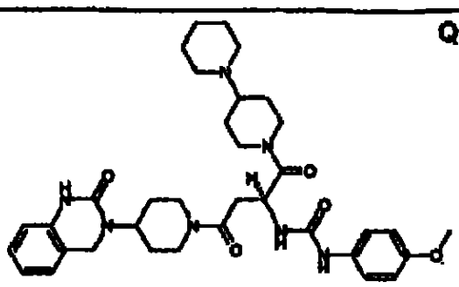
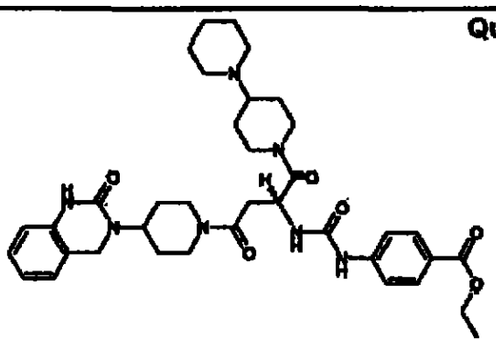
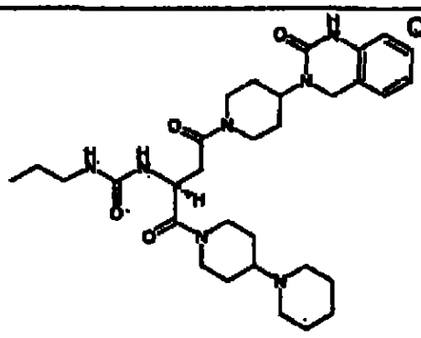
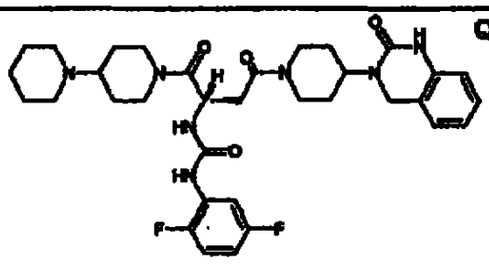
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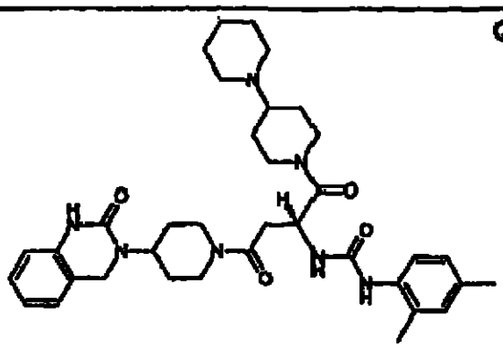
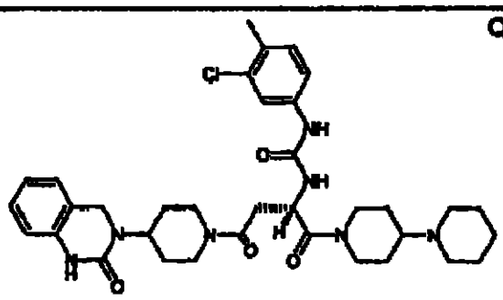
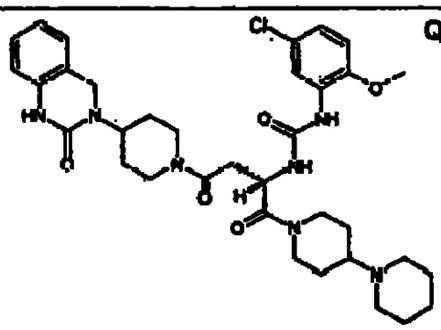
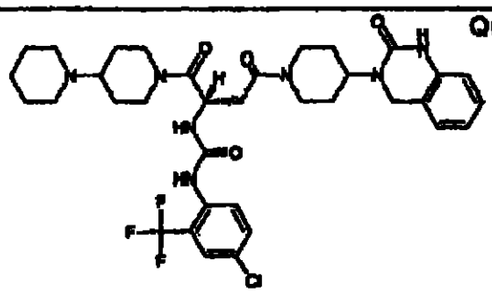
Ejemplo	Estructura	CLAR t_R (min)	EM $(MH)^+$
168	Quiral 	1.35	669.75
169	Quiral 	1.24	649.86
170	Quiral 	1.11	639.8

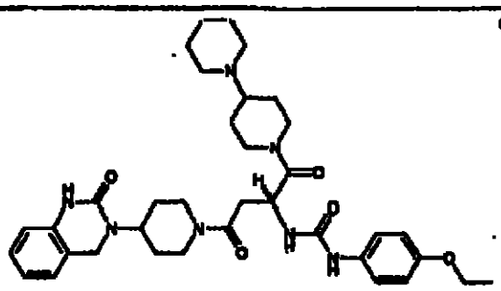
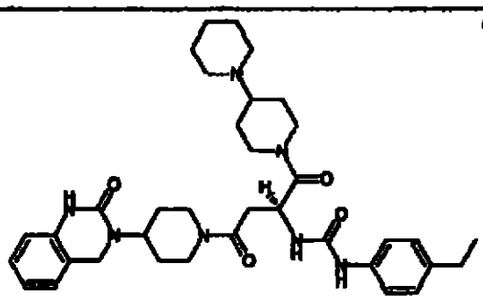
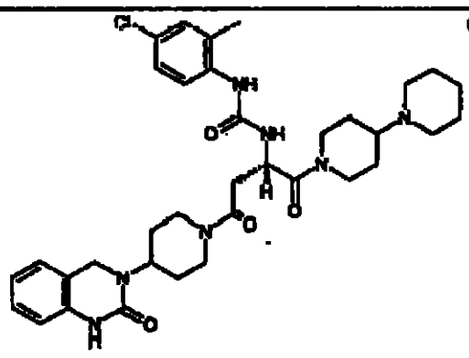
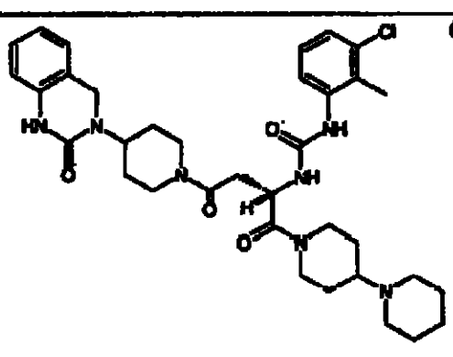
Ejemplo	Estructura	CLAR C t_R (min)	EM (MH)$^+$
171	Quiral 	1.31	633.77
172	Quiral 	1.34	650.22
173	Quiral 	1.47	684.67
174	Quiral 	1.27	675.83

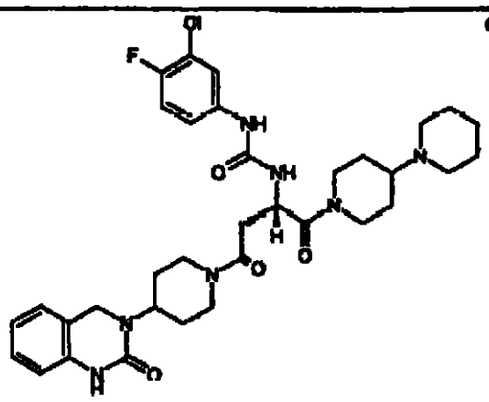
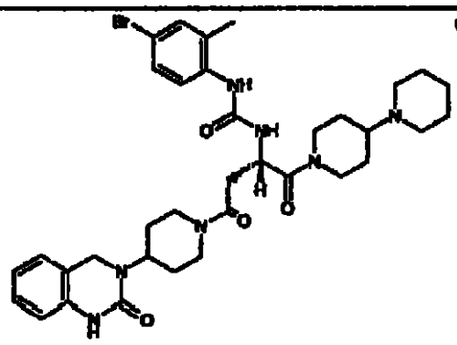
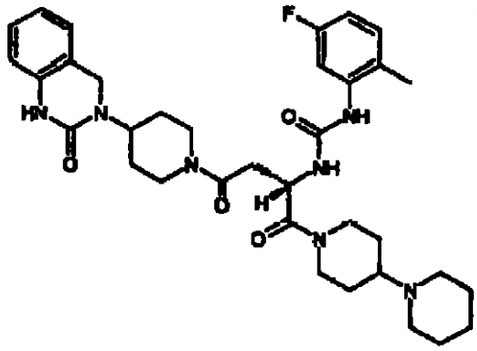
Ejemplo	Estructura	CLAR C t_R (min)	EM $(MH)^+$
175	Quiral 	1.34	659.83
176	Quiral 	1.41	694.68
177	Quiral 	1.28	633.77

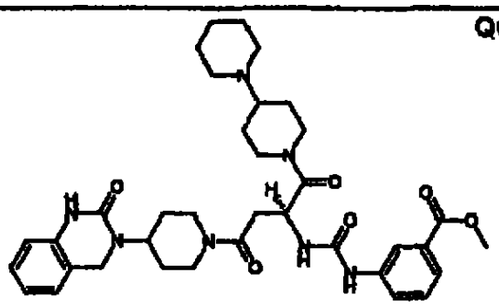
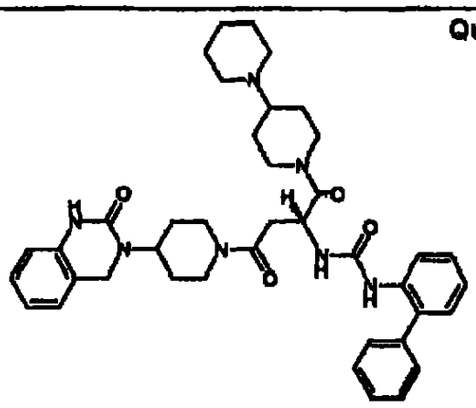
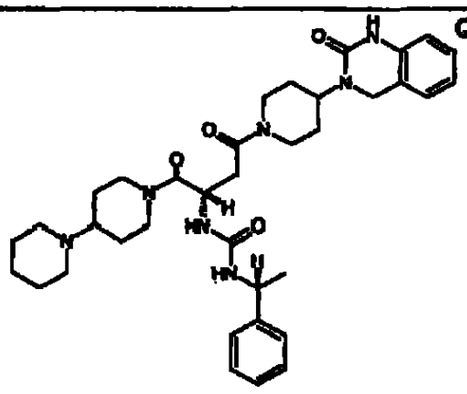
Ejemplo	Estructura	CLAR C_{tr} (min)	EM $(MH)^+$
178	 Quiral	1.39	650.22
179	 Quiral	1.42	694.68
180	 Quiral	1.26	633.77

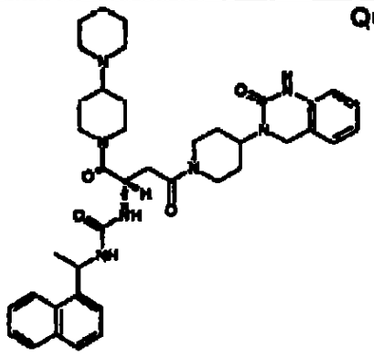
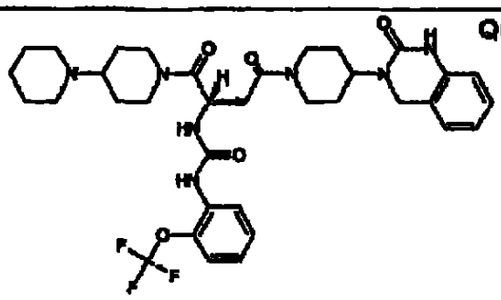
Ejemplo	Estructura	CLAR C_{tR} (min)	EM $(MH)^+$
181	Quiral 	1.19	645.81
182	Quiral 	1.34	687.84
183	Quiral 	1.08	581.76
184	Quiral 	1.31	651.76

Ejemplo	Estructura	CLAR C t_R (min)	EM $(MH)^+$
185	Quiral 	1.39	643.83
186	Quiral 	1.33	664.25
187	Quiral 	1.41	680.25
188	Quiral 	1.48	718.22

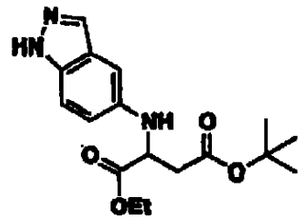
Ejemplo	Estructura	CLAR C t_R (min)	EM $(MH)^+$
189		1.28	659.83
190		1.41	643.83
191		1.41	664.25
192		1.41	664.25

Ejemplo	Estructura	CLAR C t_R (min)	EM $(MH)^+$
193	 Cloral	1.41	668.21
194	 Chiral	1.45	708.71
195	 Chiral	1.39	647.8

Ejemplo	Estructura	CLAR C t_R (min)	MS $(MH)^+$
196	Quiral 	1.27	673.82
197	Quiral 	1.45	691.88
198	Quiral 	1.26	643.83

Ejemplo	Estructura	CLAR C_{tR} (min)	EM $(MH)^+$
199	Quiral 	1.45	693.89
200	Quiral 	1.4	699.78

Éster 1-etilo del éster de 4-tert-butilo del ácido 2-(1H-indazol-5-ilamino)-succínico



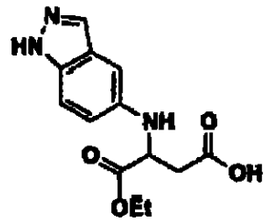
A una solución/suspensión de 5-aminoindazol (1.01 g, 7.6 mmol) en tetrahidrofurano (20 mL) se le agregó solución de glioxlato de etilo (ca. 50% en tolueno, 1.7 mL, 1.1 equiv) en una porción seguida por sulfato de magnesio (4.6 g). La mezcla se

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agitó a temperatura ambiente durante la noche (23 h) y luego se filtró y se concentró in vacuo. El intermediario de imina crudo resultante (1.3 g, 6 mmol) se secó por proceso azeotrópico con benceno anhidro y además se secó bajo alto vacío. El residuo luego se disolvió en tetrahidrofurano (20 mL) y se enfrió a 0°C. Una solución de cloruro de 2-tert-butoxi-2-oxoetilzinc (0.5 M en éter, 24 mL, 2 equiv) se agregó luego lentamente. Después de agitar a 0°C durante 1 h, la mezcla se almacenó durante la noche. La mezcla se diluyó luego con acetato de etilo y se apagó con la mitad de solución de cloruro de amonio saturada a lo largo con una cantidad mínima de HCl 0.5 N para disolver los sólidos precipitados. Las capas se separaron y la capa acuosa se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua y solución de bicarbonato de sodio saturado. La capa orgánica se secó sobre sulfato de sodio y se concentró in vacuo. El producto crudo se purificó por cromatografía de columna instantánea en gel de sílice, eluyendo con 10% metanol en cloruro de metileno, para proporcionar el producto deseado (1.3 g, 65%) como un aceite color canela (400 MHz, $CDCl_3$) δ 7.89 (1H, s), 7.40-7.27 (1H, m), 6.98-6.77 (2H, m), 4.42-4.35 (1H, m), 4.30-4.12 (3H, m), 2.80 (2H, d, J = 4.4 Hz), 1.43 (9H, s), 1.27-1.17 (4H, m), Espectro de masa: 356.24 $(M+Na)^+$, 278.23 $(M - {}^tBu)^+$, t_R = 1.287 min.

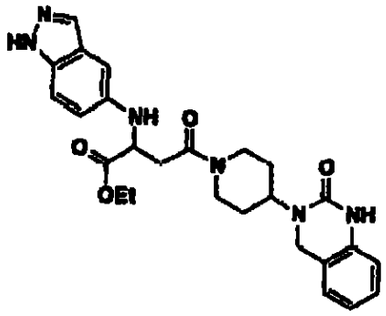
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Éster de 1-etilo del ácido 2-(1H-indazol-5-ilamino)-succínico



Una solución agitada de éster 1-etilo del éster 4-tert-butilo del ácido 2-(1H-indazol-5-ilamino)-succínico (123.6 mg, 0.37 mmol) en cloruro de metileno (2 mL) y ácido trifluoroacético (0.5 mL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó luego con acetato de etilo y se lavó con solución de cloruro de amonio saturado, agua y salmuera. La capa orgánica se secó y se concentró para dar un aceite verde oscuro: CL/EM: T_R = 0.643 min, 278.19 $(MH)^+$.

Éster de etilo del ácido 2-(1H-indazol-5-ilamino)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

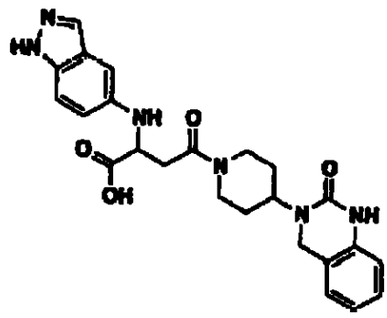


A una solución agitada de éster de 1-etilo del ácido 2-(1H-indazol-5-ilamino)-succínico (84 mg, 0.215 mmol) en cloruro

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de metileno (1 mL) se le agregó la amina (99 mg, 0.429 mmol, 2 equiv) seguido por DEPBT (128 mg, 0.43 mmol, 2 equiv.) y trietilamina (70 µL, 0.47 mmol, 2.2 equiv). La mezcla se agitó durante la noche y luego se diluyó con acetato de etilo y se lavó con la mitad de solución de cloruro de amonio saturado, agua y salmuera. La capa orgánica se secó y se concentró hasta un aceite canela. El producto crudo se purificó por cromatografía de columna instantánea en gel de sílice, eluyendo con metanol 10% en cloruro de metileno, para dar el producto deseado (32.2 mg, 34.5% durante dos etapas) como un aceite rojizo. ^{1}H-RMN (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J= 4.4 Hz), 7.33 (1H, d, J= 8.4 Hz), 7.20-7.14 (1H, m), 7.00-6.80 (4H, m), 6.70 (1H, t, J = 6.8 Hz), 4.58-4.48 (1H, m), 4.65-4.40 (2H, m), 4.34-4.05 (3H, m), 4.02-3.82 (1H, m), 3.20-2.99 (2H, m), 2.99-2.84 (1H, m), 2.70-2.52 (1H, m), 1.80-1.50 (5H, m), 1.35-1.12 (5H, m). CL/EM: t_R = 1.130 min, 491.37 $(MH)^+$.

Ácido 2-(1H-indazol-5-ilamino)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico

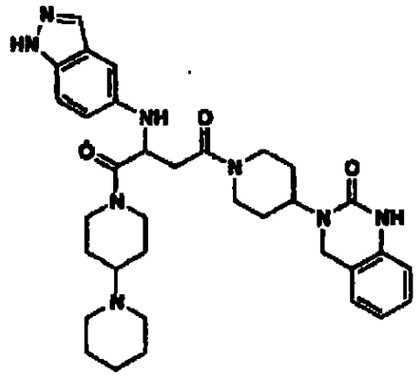


A una solución del éster de etilo (34 mg, 0.069 mmol) en

tetrahidrofurano (0.3 mL) se le agregó hidróxido de litio en agua (1M, 280 µL, 4 equiv) y la mezcla se agitó a temperatura ambiente durante 17 h. La solución se secó bajo una corriente de nitrógeno. Al residuo se le agregó tettrahidrofurano 0.2 mL y benceno anhidro 0.2 mL y la suspensión se secó soplando nuevamente con una corriente de nitrógeno. CL/EM: t_R = 0.900 min, 463.30 $(MH)^+$.

Ejemplo 201

(±)-1-[1,4']Bipiperidinil-1'-il-2-(1H-indazol-5-ilamino)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona



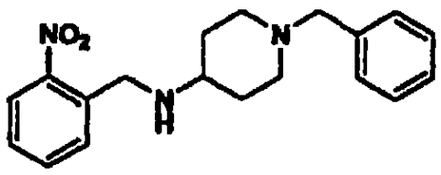
A una solución de éster de etilo del ácido 2-(1H-indazol-5-ilamino)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butírico (0.069 mmol) en dimetilformamida (0.5 mL) en un vial redondo tapado se le agregó piperidinilpiperidina (14.3 mg, 0.076 mmol, 1.1 equiv), DEPBT (22.8 mg, 1.1 equiv) y trietilamina (8 gotas, ca. 160 µL). La mezcla se agitó a temperatura ambiente durante la noche. El producto final se purificó por CLAR preparativa para proporcionar el producto deseado (15 mg, 26%

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durante dos etapas) como un sólido color canela. CL/EM: t_R = 0.917 min, 613.54 $(MH)^+$.

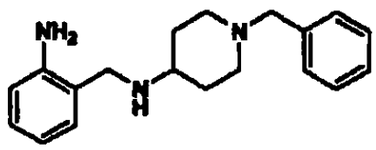
Ejemplos Adicionales

(1-bencil-piperidin-4-il)-(2-nitrobencil)-amina



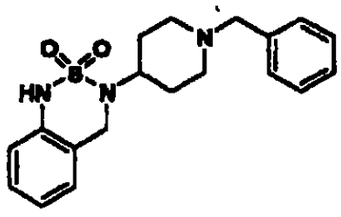
El 2-nitrobenzaldehído (1 g, 6.61 mmol) y 4-amino-1-bencilpiperidina (1.35 mL, 6.61 mmol) se combinaron en etanol (20 mL). La suspensión resultante se agitó a temperatura ambiente durante 20 min antes de agregar una solución de borohidruro de sodio (0.25 g, 6.61 mmol) en etanol (5 mL) gota a gota durante 10 min. Después de que la adición se completó, la reacción se agitó durante 1 h, se enfría hasta 0°C y se agregó cloruro de amonio concentrado a la mezcla de reacción hasta que no se observa burbujeo. Los solventes se evaporaron in vacuo y la mezcla cruda resultante se disolvió en agua (10 mL) y cloruro de metileno (10 mL). Las capas se separaron y la capa orgánica se lava con agua (2x) y salmuera (2x), se secó sobre sulfato de sodio, se filtró, y se concentró para proporcionar 1.5 g (70%) del producto deseado. CL/EM: rt = 7 min, 326.18 $(MH)^+$.

(2-Amino-bencil)-(1-bencil-piperidin-4-il)-amina



La (1-bencil-piperidin-4-il)-(2-nitro-bencil)-amina (1.2 g, 3.7 mmol) y polvo de zinc (1 g, exceso) se combinaron en ácido cítrico acuoso al 75% (16 mL) y se agitó a 60°C durante 2 h. Después de enfriar a temperatura ambiente, los solventes se removieron in vacuo y el crudo resultante se disuelve en agua (10 mL), seguido por la adición de hidróxido de amonio hasta que se alcanza un pH 3. La solución se extrajo con cloruro de metileno (3x). Las capas orgánicas se agrupan en conjunto, se lavan con agua (2x), salmuera (2x), se secan sobre sulfato de sodio, se filtran, y se concentran para proporcionar 0.8 g (73%) del producto deseado. ^{1}H-RMN (CD_3OD) δ 2.50 (m, 2H), 3.20 (m, 2H), 3.49 (dd, J=7.0, 7.3, 1H), 3.62 (m, 4H), 4.20 (s, 2H), 4.36 (s, 2H), 7.04 (m, 2H), 7.32 (dd, J=7.3, 7.6, 1H), 7.41 (d, J=7.9, 1H), 7.50 (m, Espectro de masa: 296.40 $(MH)^+$.

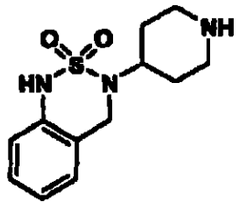
3-(1-Bencil-piperidin-4-il)-3,4-dihidro-1H-benzo[1,2,6]tiadiazin-2,2-dióxido



PT 697

Una solución de (2-amino-bencil)-(1-bencil-piperidin-4-il)-amina (1.0 g, 3.39 mmol) y sulfamida (0.64 g, 6.78 mmol) en piridina se calentó a reflujo durante 14 h. Después de enfriar a temperatura ambiente, el solvente se evaporó y el producto crudo se disuelve en agua. Después de ajustar hasta pH 9 con hidróxido de sodio 6N, la mezcla resultante se extrajo con cloruro de metileno (2x). Los extractos se lavaron con agua (2x), se secó sobre sulfato de sodio, se filtró, y se concentró para proporcionar un residuo aceitoso el cual se disolvió en acetato de etilo (4 mL). Esta solución se mezcló con HCl 4N en 1,4-dioxano (2 mL) seguido por la adición de dietil éter hasta que la precipitación del producto se presenta. El producto deseado se obtuvo por filtración para proporcionar 0.7 g (53%). CL/EM: tr = 0.96 min, 358.16 $(MH)^+$.

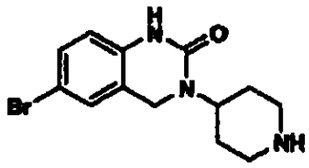
3-Piperidin-4-il-3,4-dihidro-1H-benzo[1,2,6]tiadiazina-2,2-dióxido



El 3-(1-bencil-piperidin-4-il)-3,4-dihidro-1H-benzo[1,2,6]tiadiazina-2,2-dióxido (0.46 g, 1.29 mmol) en metanol (10 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 46 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno

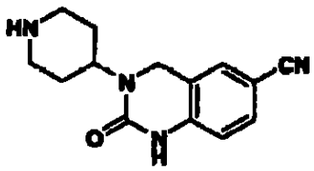
durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 0.26 g (75%) del material deseado. ^{1}H-RMN (CD_3OD) δ 1.53-1.61 (m, 2H), 1.80 (m, 2H), 2.55 (m, 2H), 2.95-3.05 (m, 2H), 3.30 (m, 2H), 3.70 (m, 2H), 4.65 (s, 2H), 6.70 (d, J=7.9, 1H), 7.40 (dd, J=8.2, 6.7, 1H), 7.10 (m, 2H). Espectro de masa: 268.10 $(MH)^+$.

6-Bromo-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona



La 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (0.2 g, 0.87 mmol) se disolvió en ácido acético (2 mL). A esta solución se le agregó una solución de bromo (1.8 mL, 35.14 mmol) en ácido acético (0.5 mL) gota a gota durante 5 min. Después de agitar a temperatura ambiente durante 1 h, la mezcla de reacción se diluyó con cloruro de metileno, se lava con agua (2x), salmuera (2x), se secó sobre sulfato de sodio, se filtró, y se concentró para proporcionar 0.16 g (59%) que se usó inmediatamente sin purificación adicional. CL/EM: tR = 0.91 min, 310.15 $(MH)^+$.

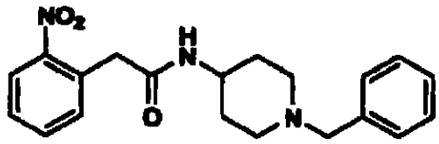
2-oxo-3-piperidin-4-il-1,2,3,4-tetrahidro-quinazolin-6-carbonitrilo



6-bromo-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona

(0.16 g, 0.52 mmol), cianuro de zinc (37 mg, 0.31 mmol) y tetraquis(trifenilfosfina)paladio (0) (60 mg, 0.05 mmol) se combinaron en dimetilformamida (4 mL). El matraz de reacción se conectó a alto vacío y se desgasificó (3x) por un método de congelado-descongelado, antes de calentarse a 90°C con agitación bajo nitrógeno durante 1 h. Después de enfriar a temperatura ambiente, la solución se evaporó in vacuo y la mezcla cruda se purificó por CLAR preparativa para proporcionar 50 mg (38%) del nitrilo deseado. ^{1}H-RMN (CD_3OD) δ 1.99 (m, 2H), 2.08-2.23 (m, 2H), 3.15 (m, 2H), 3.50 (bs, 1H), 3.55 (bs, 1H), 4.40 (m, 1H), 4.47 (s, 2H), 6.93 (d, J=8.1, 1H), 4.10 (m, 2H). Espectro de masa: 257.13 $(MH)^+$.

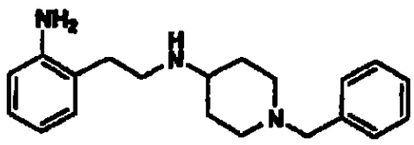
N-(1-Bencil-piperidin-4-il)-2-(2-nitro-fenil)-acetamida



El ácido (2-nitro-fenil)-acético (2.0 g, 11.04 mmol), 4-amino-1-bencilpiperidina (2.25 mL, 10.03 mmol), 1-hidroxibenzotriazol (1.49 g, 11.04 mmol) y carbodiimida de 1-(3-dimetilaminopropil)-3-etilo (2.3 g, 12.03 mmol) se combinaron en acetato de etilo (25 mL). A esta solución se le agregó trietilamina (4.2 mL. 30.1 mmol) y la mezcla de reacción se agitó a 40°C durante 2 h. Después de enfriar a temperatura ambiente, la mezcla se diluyó con acetato de etilo y se lava con agua (2x), bicarbonato de sodio al 5%,

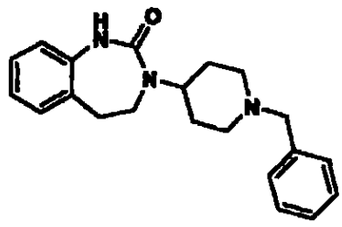
salmuera (2x), se secó sobre sulfato de sodio, y se concentró para proporcionar 3.5 g (98%) del producto deseado. CL/EM: tR = 1.24 min, 354.30 $(MH)^+$.

[2-(2-Amino-fenil)-etil]-(1-bencil-piperidin-4-il)-amina



En un matraz secado a la flama, la N-(1-bencil-piperidin-4-il)-2-(2-nitro-fenil)-acetamida (3.2 g, 9.06 mmol) e hidruro de aluminio litio (1.0 g, 18.12 mmol) se combinaron. El 1,4-dioxano (15 mL) se agregó y la mezcla lentamente se llevó hasta reflujo durante 1 h y se agitó a reflujo durante 16 h. La mezcla de reacción se enfrió hasta 0°C y el exceso de hidruro de litio aluminio se destruye por la adición gota a gota de metanol, seguido por adición cuidadosa de hidróxido de potasio al 20%. Las sales de aluminio se filtraron, el filtrado se concentró y se usó como en la siguiente reacción.

3-(1-bencil-piperidin-4-il)1,3,4,5-tetrahidro-benzo[d][1,3]diazepin-2-ona

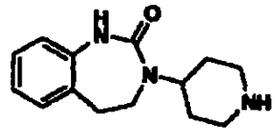


Una solución agitada de [2-(2-amino-fenil)-etil]-(1-

bencil-piperidin-4-il)-amina (0.44 g, 1.42 mmol) en tetrahidrofurano (5 mL) a 0°C se trató con diimidazol carbonilo (0.23 g, 1.42 mmol). La reacción se agitó durante 30 min a 0°C y a reflujo durante 1 h. Después de enfriar a temperatura ambiente, el solvente se evaporó y el residuo se purificó por columna para proporcionar 100 mg (21%) del producto deseado.

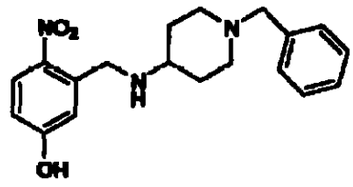
CL/EM: tR = 1.29 min, 336.34 $(MH)^+$.

3-Piperidin-4-il-1,3,4,5-tetrahidro-benzo[d][1,3]diazepin-2-ona



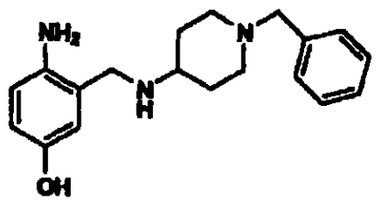
La 3-(1-bencil-piperidin-4-il)1,3,4,5-tetrahidro-benzo[d][1,3]diazepin-2-ona (100 mg, 0.3 mmol) en metanol (5 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 10 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 50 mg (68%) del material deseado. CL/EM: tR = 1.07 min, 246.26 $(MH)^+$.

3-[(1-bencil-piperidin-4-il-amino)-metil]-4-nitro-fenol



El 5-hidroxi-2-nitro-benzaldehído (5 g, 29.9 mmol) y 4-amino-1-bencilpiperidina (5.6 mL, 29.9 mmol) se combinaron en etanol (30 mL). La suspensión resultante se agitó a temperatura ambiente durante 20 min antes de agregar una solución de borohidruro de sodio (1.13 g, 29.9 mmol) en etanol (10 mL) gota a gota durante 10 min. Después de que la adición se completó, la reacción se agitó a temperatura ambiente durante 1 h, se enfría hasta 0°C y se agregó cloruro de amonio concentrado a la mezcla de reacción hasta que no se observa burbujeo. Los solventes se evaporaron in vacuo y la mezcla cruda resultante se disolvió en agua (30 mL) y cloruro de metileno (40 mL). Las capas se separaron y la capa orgánica se lava con agua (2x), salmuera (2x), se secó sobre sulfato de sodio, se filtró, y se concentró para proporcionar 5.8 g (57%) del producto deseado. CL/EM: tR = 0.95 min, 342.27 $(MH)^+$.

4-Amino-3-[(1-bencil-piperidin-4-il-amino)-metil]-fenol

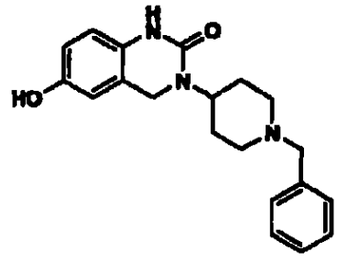


La (1-bencil-piperidin-4-il)-(2-nitro-bencil)-amina (0.25 g, 0.7 mmol) y polvo de zinc (0.2 g, exceso) se combinaron en ácido cítrico acuoso al 75% (8 mL) y se agitó a

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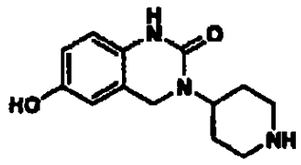
60°C durante 2 h. Después de enfriar a temperatura ambiente, los solventes se removieron in vacuo y la mezcla cruda resultante se disuelve en agua (10 mL), seguido por la adición de hidróxido de amonio hasta que se alcanza un pH 3. La solución se extrajo con cloruro de metileno (3x). Las capas orgánicas se agrupan en conjunto, se lavan con agua (2x), salmuera (2x), se secan sobre sulfato de sodio, se filtran, y se concentran para proporcionar 0.18 g (79%) del producto deseado.

3-(1-fenil-piperidin-4-il)-6-hidroxi-3,4-dihidro-1H-quinazolin-2-ona



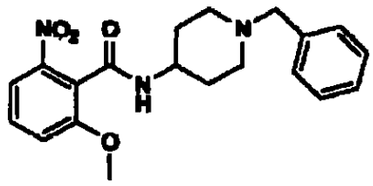
Una solución agitada de 4-amino-3-[(1-bencil-piperidin-4-il-amino)-metil]-fenol (0.16 g, 0.51 mmol) en tetrahidrofurano (3 mL) a 0°C se trató con diimidazol carbonilo (52 mg, 0.51 mmol). La reacción se agitó durante 30 min a 0°C y a reflujo durante 1 h. Después de enfriar a temperatura ambiente, el solvente se evaporó y el residuo se purificó por columna para proporcionar 100 mg (57%) del producto deseado. CL/EM: tR = 1.09 min, 338.28 $(MH)^+$.

6-Hidroxi-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona



La 3-(1-bencil-piperidin-4-il)-6-hidroxi-3,4-dihidro-1H-quinazolin-2-ona (100 mg, 0.3 mmol) en metanol (5 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 10 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 60 mg (81%) del material deseado. CL/EM: tR = 0.75 min, 248.22 $(MH)^+$.

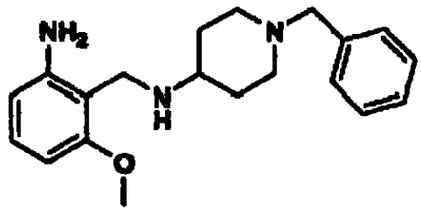
N-(1-Bencil-piperidin-4-il)-2-metoxi-6-nitro-benzamida



El ácido 2-metoxi-6-nitro-benzoico (2.0 g, 10.1 mmol), 4-amino-1-bencilpiperidina (1.9 mL, 10.1 mmol), 1-hidroxibenzotriazol (1.43 g, 10.5 mmol) y 1-(3-dimetilaminopropil)-3-etil carbodiimida (1.9 g, 10.1 mmol) se combinaron en acetato de etilo (25 mL). A esta solución se le agregó trietilamina (4.2 mL. 30.3 mmol) y la mezcla de reacción se agita a durante 2 h. Después

de enfriar a temperatura ambiente, la mezcla se diluyó con acetato de etilo y se lava con agua (2x), bicarbonato de sodio al 5%, salmuera (2x), se secó sobre sulfato de sodio, y se concentró para proporcionar 3.2 g (86%) del producto deseado. CL/EM: tR = 1.10 min, 370.28 $(MH)^+$.

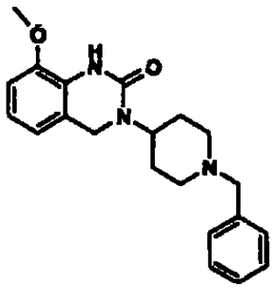
(2-Amino-6-metoxi-bencil)-(1-bencil-piperidin-4-il)-amina



En un matraz secado a la flama, se combinaron N-(1-bencil-piperidin-4-il)-2-metoxi-6-nitro-benzamida (1.0 g, 2.8 mmol) e hidruro de litio aluminio (0.31 g, 8.45 mmol). A la mezcla se le agregó 1,4-dioxano anhidro (15 mL). La mezcla lentamente se llevó hasta reflujo durante 1 h y se agitó a reflujo durante 16 h. La mezcla de reacción se enfrió hasta 0°C y el exceso hidruro de litio aluminio se destruye por adición gota a gota de metanol, seguido por adición cuidadosa de hidróxido de potasio al 20%. Las sales de aluminio se filtraron, el filtrado se concentró y se usó como en la siguiente reacción.

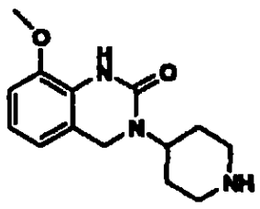
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3-(1-bencil-piperidin-4-il)-8-metoxi-3,4-dihidro-1H-quinazolin-2-ona



Una solución agitada de (2-amino-6-metoxi-bencil)-(1-bencil-piperidin-4-il)-amina (0.2 g, 0.62 mmol) en tetrahidrofurano (3 mL) a 0°C se trató con diimidazol carbonilo (99 mg, 0.62 mmol). La reacción se agitó durante 30 min a 0°C y a reflujo durante 1 h. Después de enfriar a temperatura ambiente, el solvente se evaporó y el residuo se purificó por columna para proporcionar 150 mg (68%) del producto deseado. CL/EM: tR = 1.41 $(MH)^+$.

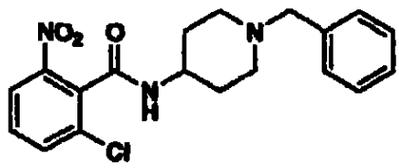
8-Metoxi-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona



La 3-(1-bencil-piperidin-4-il)-8-metoxi-3,4-dihidro-1H-quinazolin-2-ona (100 mg, 0.28 mmol) en metanol (5 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 10 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La

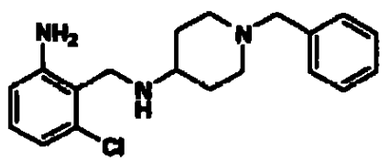
reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 68 mg (93%) del material deseado. CL/EM: tR = 1.11 min, 262.23 $(MH)^+$.

N-(1-bencil-piperidin-4-il)-2-cloro-6-nitro-benzamida



El ácido 2-cloro-6-nitro-benzoico (1.2 g, 5.97 mmol), 4-amino-1-bencilpiperidina (1.1 mL, 5.97 mmol), 1-hidroxibenzotriazol (0.84 g, 1.05 equiv) y 1-(3-dimetilaminopropil)-3-etil carbodiimida (1.1 g, 1.05 equiv) se combinaron en acetato de etilo (20 mL). A esta solución se le agregó trietilamina (2.5 mL. 3.0 equiv) y la mezcla de reacción se agita a 40°C durante 2 h. Después de enfriar a temperatura ambiente, la mezcla se diluyó con acetato de etilo y se lava con agua (2x), bicarbonato de sodio al 5%, salmuera (2x), se secó sobre sulfato de sodio, y se concentró para proporcionar 1.9 g (85%) del producto deseado.

(2-Amino-6-cloro-bencil)-(1-bencil-piperidin-4-il)-amina

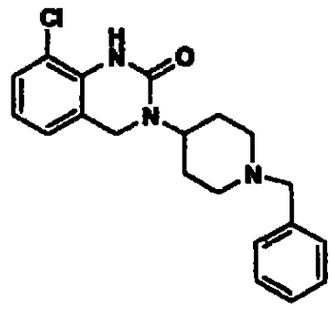


En un matraz secado a la flama, la N-(1-bencil-

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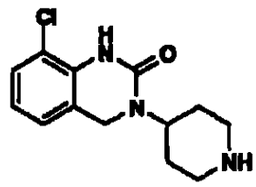
piperidin-4-il)-2-cloro-6-nitro-benzamida (1.67 g, 4.47 mmol) e hidruro de litio aluminio (0.51 g, 13.43 mmol) se combinaron. A esto se agregó 1,4-dioxano anhidro (15 mL). La mezcla lentamente se llevó hasta reflujo y se agitó durante 16 h. La mezcla de reacción se enfrió hasta 0°C y el exceso de hidruro de litio aluminio se destruye por la adición gota a gota de metanol, seguido por adición cuidadosa de hidróxido de potasio al 20%. Las sales de aluminio se filtraron, el filtrado se concentró y se usó como en la siguiente reacción.

3-(1-bencil-piperidin-4-il)-8-cloro-3,4-dihidro-1H-quinazolin-2-ona



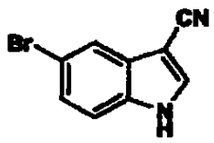
Una solución agitada de (2-amino-6-cloro-bencil)-(1-bencil-piperidin-4-il)-amina (0.66 g, 2.0 mmol) en tetrahidrofurano (8 mL) a 0°C se trató con diimidazol carbonilo (0.36 g, 2.05 mmol). La reacción se agitó por 30 min a 0°C y a reflujo durante 1 h. Después de enfriar a temperatura ambiente, el solvente se evaporó y el residuo se purificó por columna para proporcionar 0.58 g (82%) del producto deseado. CL/EM: tR = 1.40 min, 356.25 $(MH)^+$.

2-cloro-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona



La 3-(1-bencil-piperidin-4-il)-8-cloro-3,4-dihidro-1H-quinazolin-2-ona (0.17 g, 0.48 mmol) en metanol (10 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 17 mg). El ácido trifluoroacético (0.2 mL) se agregó y la mezcla se mojó con nitrógeno luego se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 100 mg (79%) del material deseado. CL/EM: tR = 0.99 min, 266.08 $(MH)^+$.

5-bromo-1H-indol-3-carbonitrilo

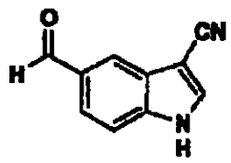


Una mezcla de 5-bromo-indol-3-carboxaldehído (5 g, 22.3 mmol) fosfato ácido de diamonio (15.6 g, 31.8 mmol) en 1-nitropropano (66 mL) y ácido acético (22 mL) se calentaron a reflujo durante 16 h. Después de enfriar a temperatura ambiente, los solventes se removieron bajo presión reducida y se agregó agua al residuo oscuro. Después de una corta espera, se precipitó rápidamente. El sólido se filtró, se

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lava varias veces con agua y se seca durante varias horas para proporcionar 4.3 g (86%) del producto deseado. ^{1}H-RMN (CD_3OD) δ 7.40 (m, 2H), 7.77 (s, 1H), 7.97 (s, 1H). Espectro de masa: 222.95 $(MH)^+$.

5-Formil-1H-indol-3-carbonitrilo

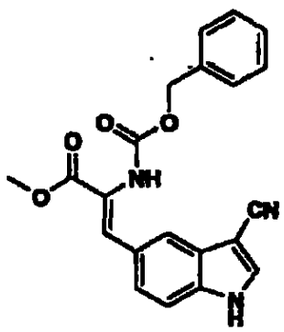


El 5-bromo-1H-indol-3-carbonitrilo (4.25 g, 19.23 mmol) e hidruro de sodio (0.51 g, 21.2 mmol) se pesaron en un matraz de fondo redondo secado a la flama que contiene una barra agitadora magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, el tetrahidrofurano seco (24 mL) se agregó. La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante lo cual se vuelve homogénea. La mezcla agitada se enfrió hasta -78°C y una solución de sec-butillitio en ciclohexano (1.4M, 30.2 mL, 2.2 equiv) se agregó durante varios minutos. Después de 1 h a -78°C, la dimetilformamida (6.0 mL) se agregó lentamente y la mezcla se permitió que se entibiara a temperatura ambiente durante la noche. La solución se enfrió hasta 0°C y se trató cuidadosamente con ácido clorhídrico 1 N (45 mL). Después de algunos minutos, se agregó bicarbonato de sodio sólido hasta que se alcanza un pH de 9-10. Las dos capas se separaron y la fase acuosa se lava dos veces con acetato de etilo. Las capas

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orgánicas combinadas se lavaron con agua (2x), salmuera (2x), se secaron sobre sulfato de sodio, y se concentraron. La cromatografía de columna dio 2.4 g (72%) de material puro. CL/EM: tR = 171.07 $(MH)^+$.

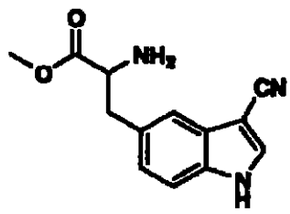
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(3-ciano-1H-indol-5-il)-acrílico



Una solución agitada de éster de trimetilo de N-benciloxicarbonil-α-fosfonoglicina (1.68 g, 5.1 mmol) en tetrahidrofurano (10 mL) a temperatura ambiente se trató con tetrametilguanidina (0.6 mL, 1.1 equiv). Después de 10 min, el 5-formil-1H-indol-3-carbonitrilo (0.72 g, 4.24 mmol) se agregó. Después de agitar a temperatura ambiente durante 3 días, el solvente se evaporó y el residuo se lava con agua (2x), salmuera (2x), se secó sobre sulfato de sodio, y se concentró. La cromatografía de columna dio 1.3 g (82%) de material puro. CL/EM: tR = 1.43 min, 376.22 $(MH)^+$.

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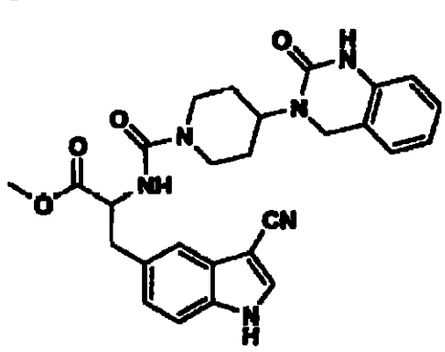
Éster de metilo del ácido (±)-2-amino-3-(3-ciano-1H-indol-5-il)-propiónico



El éster de metilo del ácido 2-benciloxicarbonilamino-3-(3-ciano-1H-indol-5-il)-acrílico (0.5 g, 1.3 mmol) en metanol (8 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 50 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 0.3 g (92%) del material deseado. CL/EM: tR = 0.80 min, 244.20 $(MH)^+$.

Ejemplo 202

éster de metilo del ácido (±)-3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

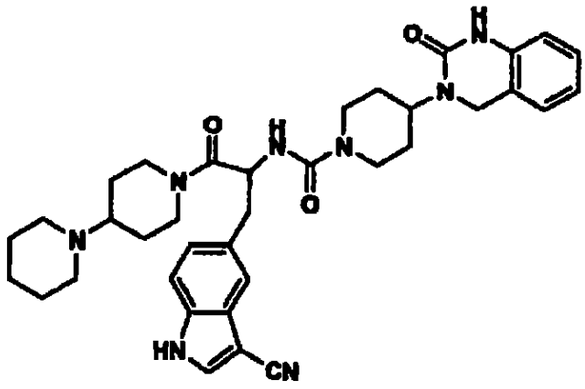


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Una solución agitada del éster de metilo del ácido 2-amino-3-(3-ciano-1H-indol-5-il)-propiónico (25 mg, 0.11 mmol) en tetrahidrofurano (3 mL) a 0°C se trató con diimidazol carbonilo (17.5 mg, 1.1 equiv.). La reacción se agitó durante 5 min a 0°C, se entibia a temperatura ambiente, se agita 10 min, y se trató con 3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona (25 mg, 1.1 equiv.). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se purificó por cromatografía de columna para dar 40 mg (75%) como un polvo blanco. CL/EM: tR = 1.37 min, 501.33 $(MH)^+$.

Ejemplo 203

[2-[1,4']bipiperidinil-1'-il-1-(3-ciano-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



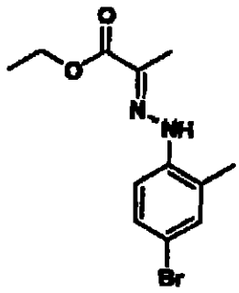
Una solución del éster de metilo del ácido 3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-

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piperidin-1-carbonil]-amino}-propiónico (15 mg, 0.03 mmol) en metanol (0.6 mL) a temperatura ambiente se trató con una solución de monohidrato de hidróxido de litio (3.0 mg, 2.5 equiv.) en agua (0.1 mL). La solución se agitó a temperatura ambiente durante 2 h. La solución se enfrió hasta 0°C, y se trató con sulfato ácido de potasio 1M acuoso (60 µL, 2.0 equiv.), y los solventes se evaporaron para dar el ácido crudo el cual se usó inmediatamente sin purificación. El ácido crudo se disolvió en dimetilformamida (0.4 mL) se enfría hasta 0°C, y se trató secuencialmente con cloruro de metileno (0.2 mL), 4-piperidil-piperidina (11 mg, 2.2 equiv), N,N-diisopropiletilamina (12 µL, 2.3 equiv) y PyBop (19 mg, 1.2 equiv). La solución se agitó durante 15 min a 0°C, se entibia a temperatura ambiente, se agitó 1.5 h, y se concentró. El producto se purificó por cromatografía de columna para dar 10.1 mg (52% 2 etapas). ^{1}H-RMN (CD_3OD) δ 1.60-2.10 (m, 14H), 2.53 (d, J=13.0, 1H), 2.58 (d, J=12.2, 1H), 2.65-3.00 (m, 7H), 3.12 (d, J=7.0, 1H), 3.17 (d, J=7.0, 1H), 3.84 (s, 1H), 3.46 (bs, 1H), 4.08-4.86 (m, 5H), 4.70 (m, 1H), 5.02 (dd, J=8.2, 6.7,1H), 6.79 (d, J=7.6, 1H), 6.9 (m, 1H), 7.10 (dd, J=7.3, 7.9, 1H), 9.18 (s, 1H), 7.15 (dd, J=7.3, 7.6, 1H), 7.30 (m, 1H), 7.50 (m, 1H), 8.00 (s, 1H). Espectro de masa: 647.41 $(MH)^+$.

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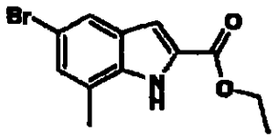
Éster de metilo del ácido 3-(4-bromo-2-metil-fenilamino)-2-metil-acrílico



A una solución de 4-bromo-2-metil anilina (7.0 g, 37.8 mmol) en acetonitrilo (80 mL) se agregó, secuencialmente, ácido clorhídrico concentrado (15 mL), agua (40 mL) y una solución de nitrato de sodio (2.74 g, 39.7 mmol) en agua (40 mL) bajo enfriamiento en hielo para dar la sal de diazonio. La solución se transfirió gota a gota a una solución de hidróxido de potasio al 50% (16 mL) y etil-2-metil acetoacetato (5.38 mL, 38 mmol) en etanol (50 mL) a 0°C. Después de que la adición se completó, la mezcla de reacción se vació en agua con hielo (150 mL) y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera (2x), se secó sobre sulfato de sodio, se filtró, y se concentró para dar 7.5 g (66%) del compuesto del título el cual se usó inmediatamente sin purificación. ^{1}H-RMN (CD_3OD) δ 1.80 (t, J=7.0, 3H), 2.13 (s, 3H), 2.29 (s, 3H), 4.26 (dd, J=5.8, 7.0, 1H), 4.30 (dd, J=5.8, 7.0, 1H), 7.26 (m, 2H), 7.43 (m, 1H). Espectro de masa: 323.07 $(MNa)^+$.

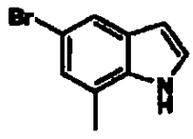
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Éster de etilo del ácido 5-bromo-7-metil-1H-indol-2-carboxílico



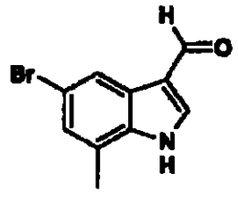
Una solución de monohidrato de ácido p-toluensulfónico (4.26 g, 75 mmol) en tolueno (80 mL) se calentó a reflujo bajo un separador de agua dean-stark por 1.5 h. A esta solución se le agregó una solución de éster de etilo del ácido 5-bromo-7-metil-1H-indol-2-carboxílico (7.5 g, 25.0 mmol) en tolueno (40 mL) y la mezcla de reacción se calentó a reflujo durante 5 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se vació en agua con hielo (120 mL) y se extrajo dos veces con acetato de etilo. Las capas orgánicas se agrupan en conjunto y se lava con bicarbonato de sodio (2x), salmuera (2x), se secó sobre sulfato de sodio, se filtró, y se concentró. La cromatografía de columna en gel de sílice proporciona 5.5 g (78%) del compuesto del título. ^{1}H-RMN (CD_3OD) δ 1.35 (t, J=7.0, 3H), 2.52 (s, 3H), 4.36 (q, J=7.0, 2H), 7.13 (s, 1H), 7.14 (s, 7.70 (s, 1H), 11.90 (s, 1H). Espectro de masa: 284.09 $(MH)^+$.

5-Bromo-7-metil-1H-indol



El éster de etilo del ácido 5-bromo-7-metil-1H-indol-2-carboxílico (5.3 g, 18.7 mmol) se agregó a una solución de hidróxido de potasio en mezcla de agua/etanol 1:1 (20 mL) y se calentó a reflujo durante 12 h. Después de enfriar a temperatura ambiente, los solventes se removieron in vacuo y el residuo resultante se transfiere a una solución de ácido clorhídrico 6N (20 mL). El precipitado blanco que se forma se filtró, se lava varias veces con agua, y se seca durante varias horas. El sólido crudo se disolvió en quinolina (14 mL) y se calentó a reflujo durante 4 h. Después de enfriar a temperatura ambiente, la mezcla cruda se vació en una mezcla de agua con hielo (100 mL) y ácido clorhídrico concentrado (16 mL), se extrajo con acetato de etilo (2x), salmuera (2x), se secó sobre sulfato de sodio, y se concentró. Los intentos para recristalizar el producto deseado del isopropanol resultan en una descomposición importante. El compuesto del título se obtuvo por la cromatografía instantánea en gel de sílice para proporcionar 1.5 g (38%, 2 etapas). CL/EM: tR = 1.72 min, 210.05 $(MH)^+$.

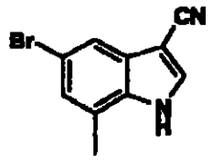
5-bromo-7-metil-1H-indol-3-carboxaldehído



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El 5-bromo-7-metil-1H-indol (1.2 g, 5.71 mmol) se disolvió en acetonitrilo (6 mL) y se transfiere lentamente a una solución de bromuro de bromometilen dimetil amonio (1.36 g, 6.28 mmol) en acetonitrilo (9 mL) a -10°C hasta 0°C. La reacción se agitó a 0°C durante 2 horas y a temperatura ambiente durante 30 min. Los solventes se evaporaron y la mezcla cruda se disuelve en agua y se agitó a 50°C por 4 h. Después de enfriar a temperatura ambiente, la mezcla cruda se extrajo con acetato de etilo (2x). Las capas orgánicas se agrupan en conjunto y se lavan con salmuera (2x), se secan sobre sulfato de magnesio, se filtran, y se concentran. La purificación por cromatografía instantánea en gel de sílice proporciona 0.7 g (52%, 2 etapas) del compuesto deseado. ^{1}H-RMN (CD_3OD) δ 2.50 (s, 3H), 7.24 (s, 1H), 8.34 (m, 1H), 9.93 (s, 1H). Espectro de masa: 238.05 $(MH)^+$.

5-bromo-7-metil-1H-indol-3-carbonitrilo

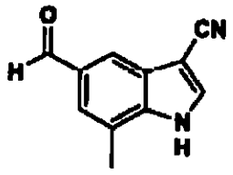


Una mezcla de 5-bromo-indol-3-carboxaldehído (0.7 g, 2.94 mmol), fosfato ácido de amonio (2.05 g, 5 mmol) en 1-nitropropano (9 mL) y ácido acético (3 mL) se calentaron a reflujo durante 16 h. Después de enfriar a temperatura ambiente, los solventes se removieron bajo presión reducida y se agregó agua al residuo oscuro. Después de una corta

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espera, el 5-bromo-1H-indol-3-carbonitrilo se precipitó rápidamente, se filtró, se lava varias veces con agua y se seca durante varias horas para proporcionar 0.6 g (87%) del nitrilo deseado. CL/EM: tR = 1.71 min, 235.01 $(MH)^+$.

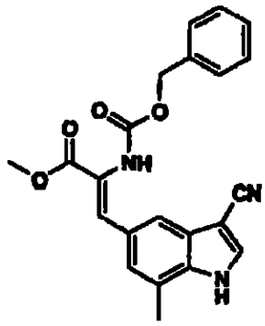
5-formil-7-metil-1H-indol-3-carbonitrilo



El 5-bromo-7-metil-1H-indol-3-carbonitrilo (0.58 g, 2.46 mmol) e hidruro de sodio (68 mg, 2.7 mmol) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra agitadora magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, se agregó tetrahidrofurano seco (9 mL). La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante lo cual se vuelve homogénea. La mezcla agitada se enfrió hasta -78°C y una solución de sec-butillitio en ciclohexano (1.4M, 3.8 mL, 2.2 equiv) se agregó durante varios minutos. Después de 1 h a -78°C, la dimetilformamida (0.9 mL) se agregó lentamente y la mezcla se permitió que se entibiara hasta temperatura ambiente durante la noche. La solución se enfrió hasta 0°C y se trató cuidadosamente con ácido clorhídrico 1N. Después de algunos minutos, el bicarbonato de sodio sólido se agregó hasta que se alcanzó un pH de 9-10. Las dos capas se separaron y la fase acuosa se

lava dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua (2x), salmuera (2x), se secan sobre sulfato de sodio, y se concentran. La cromatografía de columna dio 60 mg (14%) del producto deseado y 0.4 g del material de partida sin reaccionar. CL/EM: tR = 1.21 min, 185.10 $(MH)^+$.

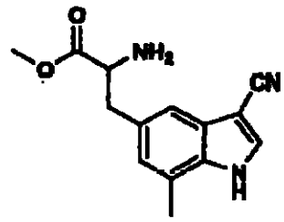
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(3-ciano-7-metil-1H-indol-5-il)-acrílico



Una solución agitada de éster de N-benciloxicarbonil-α-fosfonoglicina trimetilo (180 mg, 0.54 mmol) en tetrahidrofurano (3 mL) a temperatura ambiente, se trató con tetrametilguanidina (40 µL, 1.1 equiv). Después de 10 min, el 5-formil-7-metil-1H-indol-3-carbonitrilo (50 mg, 0.27 mmol) se agregó. Después de agitar a temperatura ambiente durante 3 días, el solvente se evaporó y el residuo se lava con agua (2x), salmuera (2x), se secó sobre sulfato de sodio, y se concentró. La cromatografía de columna dio 100 mg (95%) de material puro. CL/EM: tR = 1.59 min, 390.24 $(MH)^+$.

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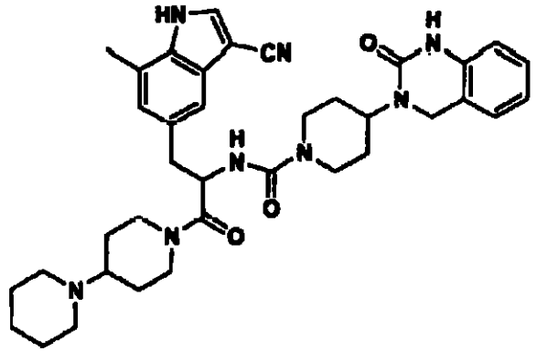
Éster de metilo del ácido (±)-2-amino-3-(3-ciano-7-metil-1H-indol-5-il)-propiónico



El éster de metilo del ácido 2-benciloxicarbonilamino-3-(3-ciano-7-metil-1H-indol-5-il)-acrílico (0.1 g, 0.26 mmol) en metanol (2.5 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 10 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 60 mg (90%) del material deseado. CL/EM: tR = 0.93 min, 258.22 $(MH)^+$.

Ejemplo 204

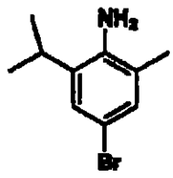
[2-[1,4']bipiperidinil-1'-il-1(3-ciano-7-metil-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



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Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD) δ 1.55-2.10 (m, 16H), 2.50 (s, 3H), 2.80-3.20 (m, 9H), 4.10-4.40 (m, 7H), 4.90 (m, 3H), 6.72 (d, J=7.9, 1H), 6.93 (dd, J=8.5, 8.5, 1H), 7.40 (s, 1H), 7.88 (s, 1H), 7.90 (s, 1H), 7.90 (s, 1H), 7.99 (s, 1H). Espectro de masa: 651.57 $(MH)^+$.

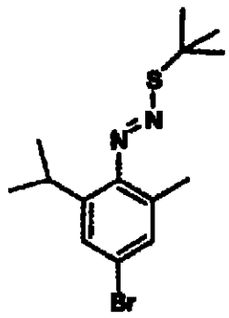
4-Bromo-2-isopropil-6-metil-fenilamina



La 2-isopropil-6-metil-fenilamina (5 g, 33.5 mmol) se disolvió en ácido acético (20 mL). A esta solución se le agregó una solución de bromo (1.8 mL, 35.14 mmol) en ácido acético (5 mL) gota a gota durante 10 min. Después de agitar durante 1 h a temperatura ambiente, la mezcla de reacción se diluyó con cloruro de metileno, se lava con agua (2x), tiosulfato de sodio saturado (2x), bicarbonato de sodio saturado (2x), y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró, y se concentró. La purificación por cromatografía instantánea en gel de sílice proporciona 7.6 g (cuantitativa) del producto deseado. CL/EM: tR = 1.37 min, 230.07 $(MH)^+$.

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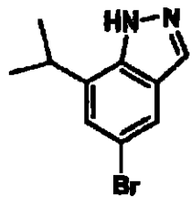
Sulfuro de 4-bromo-2-isopropil-6-metil-fenildiazo-t-butilo



La 4-bromo-2-isopropil-6-metil-fenilamina (7.6 g, 33.5 mmol) se suspendió en ácido clorhídrico al 24% (15 mL). La mezcla agitada se enfrió hasta -20°C y se trató con nitrato de sodio (2.4 g, 1.05 equiv.) en agua (5 mL), gota a gota durante 30 min mientras la temperatura se mantiene debajo de -5°C. Después de 30 min adicionales a -5°C hasta -20°C, la mezcla se amortigua hasta ca. pH 5 con acetato de sodio sólido. Esta mezcla (mantenida a ca. -10°C) se agregó en porciones a una solución agitada de t-butil tiol (3.77 mL, 1.0 equiv.) en etanol (25 mL) a 0°C durante ca. 30 min. Después de la adición, la mezcla se agitó a 0°C durante 30 min y luego se agregó hielo molido (ca. 50 mL). El sólido café ligero resultante se colectó por filtración, se lava con agua, y se seca bajo alto vacío durante varias horas para proporcionar 7.9 g (72%) del producto deseado. ^{1}H-RMN ($CDCl_3$) δ 1.15 (t, J=6.7, 3H), 1.58 (s, 9H), 2.00 (s, 3H), 2.54 (m, 1H), 7.20 (s, 1H), 7.28 (s, 1H). Espectro de masa: 331.08 $(MNa)^+$.

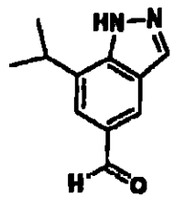
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5-Bromo-7-isopropil-1H-indazol



Un matraz de fondo redondo secado a la flama se cargó con sulfuro de 4-bromo-2,6-dietilfenildiazo-t-butilo (7.94 g, 24 mmol) y t-butóxido de potasio (27 g, 10 equiv). Una barra de agitación se agregó y la mezcla se colocó bajo nitrógeno. A esto se le agregó dimetilsulfóxido seco (70 mL). La mezcla se agitó vigorosamente durante la noche a temperatura ambiente. La mezcla de reacción se vació cuidadosamente en una mezcla de hielo molido (250 mL) y ácido clorhídrico al 10% (120 mL). La suspensión resultante se colectó por filtración y se lava varias veces con agua. El sólido se colectó y se seca in vacuo para dar 4.2 g (74%) del producto deseado. CL/EM: tR = 1.73 min, 241.06 $(MH)^+$.

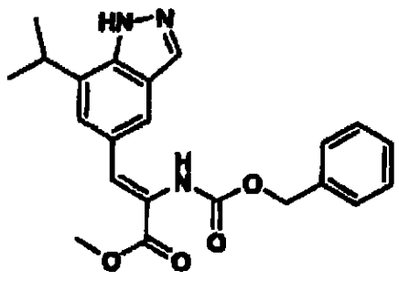
7-Isopropil-1H-indazol-5-carbaldehído



El 5-bromo-7-isopropil-1H-indazol (3.1 g, 12.1 mmol) e hidruro de sodio (0.34 g, 1.1 equiv.) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra

agitadora magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, el tetrahidrofurano seco (18 mL) se agregó. La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante lo cual se vuelve homogénea. La mezcla agitada se enfrió hasta -78°C y una solución de sec-butillitio en ciclohexano (1.4M, 20 mL, 2.2 equiv.) se agregó durante varios minutos. Después de 1 h a -78°C, la dimetilformamida (3.0 mL) se agregó lentamente y la mezcla se permitió que se entibiara a temperatura ambiente durante la noche. La solución se enfrió hasta 0°C y se trató cuidadosamente con ácido clorhídrico 1 N (35 mL). Después de algunos minutos, el bicarbonato de sodio sólido se agregó hasta que se alcanza un pH de 9-10. Las dos capas se separaron y la fase acuosa se lava dos veces con acetato de etilo. Las capas orgánicas combinadas se lavaron con agua (2x), salmuera (2x), se secaron sobre sulfato de sodio, y se concentraron. La cromatografía de columna dio 2.1 g (92%) de material puro. CL/EM: tR = 1.15 min, 189.12 $(MH)^+$.

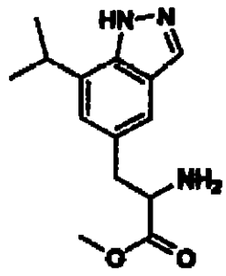
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-isopropil-1H-indazol-5-il)acrílico



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Una solución agitada de éster de trimetil N-benciloxicarbonil-α-fosfonoglicina (0.39 g, 1.2 equiv) en tetrahidrofurano (5 mL) a temperatura ambiente, se trató con tetrametilguanidina (0.16 mL, 1.1 equiv.). Después de 10 min, el 7-isopropil-1H-indazol-5-carbaldehído (0.2 g, 1.06 mmol) se agregó. Después de agitar a temperatura ambiente durante 3 días, el solvente se evaporó y el residuo se purificó por cromatografía instantánea en gel de sílice para dar 0.35 g (84%) del producto. CL/EM: tR = 1.61 min, 394.16 $(MH)^+$.

Éster de metilo del ácido (±)-2-amino-3-(7-isopropil-1H-indazol-5-il)propiónico

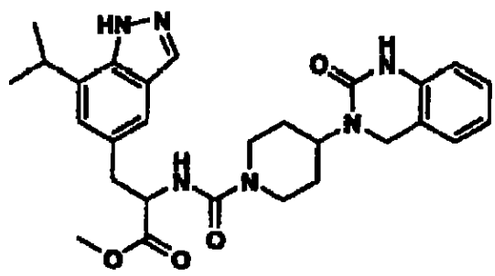


Una solución del éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-isopropil-1H-indazol-5-il)acrílico (0.35 g, 0.89 mmol) en metanol (7 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 35 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 0.21 g (90%) del material deseado.

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Ejemplo 205

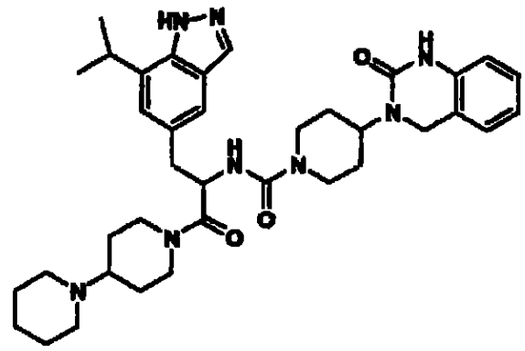
Éster de metilo del ácido (±)-3-(7-isopropil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describe arriba por el éster de metilo del ácido 3-(3-ciano-1H)-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: tR = 1.49 min, 519.35 $(MH)^+$.

Ejemplo 206

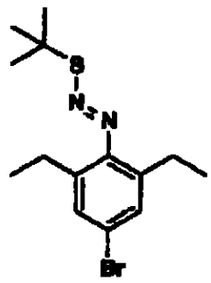
[2-[1,4']bipiperidinil-1'-il-1(7-isopropil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparado como se describe arriba por el Ejemplo 203 a

partir del éster de metilo del ácido 3-(7-isopropil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. ^{1}H-RMN (CD_3OD) δ 1.45 (m, 6H), 1.60-2.05 (m, 14H), 2.20-2.50 (m, 4H), 2.73 (d, J=13.7, 1H), 2.90 (m, 4H), 4.05 (d, J=14.0, 1H), 4.20 (m, 2H), 4.35 (s, 1H), 4.65 (dd, J=12.2, 14.3, 1H), 4.95 (m, 2H), 6.79 (d, J=7.9, 1H), 6.92 (dd, J=7.6, 6.1, 1H), 7.13 (m, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 8.05 (s, 1H). Espectro de masa: 655.40 $(MH)^+$.

Sulfuro de 4-bromo-2,6-dietilfenildiazo-t-butilo

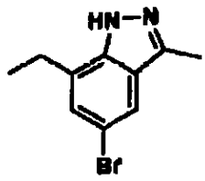


La 4-bromo-2,6-dietilanilina (6.3 g, 27.6 mmol) se suspendió en ácido clorhídrico al 24% (15 mL). La mezcla agitada se enfrió hasta -20°C y se trató con nitrato de sodio (2.0 g, 1. 05 equiv.) en agua (5 mL), gota a gota durante 30 min mientras la temperatura se mantiene debajo de -5°C. Después de 30 min adicionales a -5°C hasta -20°C, la mezcla se amortigua hasta ca. pH 5 con acetato de sodio sólido. Esta mezcla (mantenida a ca. -10°C) se agregó en porciones a una solución agitada de t-butil tiol (3.15 mL, 1.0 equiv.) en etanol (25 mL) a 0°C durante ca. 30 min. Después de la

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adición, la mezcla se agitó a 0°C durante 30 min y luego se agregó hielo molido (ca. 50 mL). El sólido café ligero resultante se colectó por filtración, se lava con agua, y se seca bajo alto vacío durante varias horas para proporcionar 6.0 g (66%) del producto deseado. ^{1}H-RMN ($CDCl_3$) δ 1.15 (t, J=7.6, 6H), 1.50 (s, 9H), 2.27 (m, 4H), 7.21 (s, 2H). Espectro de masa: 331.08 $(MH)^+$.

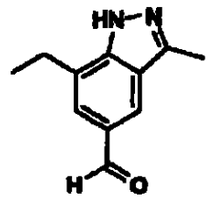
5-Bromo-7-etil-3-metilindazol



Un matraz de fondo redondo secado a la flama se cargó con sulfuro de 4-bromo-2,6-dietilfenildiazo-t-butilo (4.0 g, 12.1 mmol) y t-butóxido de potasio (13.2 g, 10 equiv). Una barra de agitación se agregó y la mezcla se coloca bajo nitrógeno. A esto se agregó dimetilsulfóxido seco (35 mL). La mezcla se agitó vigorosamente durante la noche a temperatura ambiente. La mezcla de reacción se vació cuidadosamente en una mezcla de hielo molido (130 mL) y ácido clorhídrico al 10% (60 mL). La suspensión resultante se colectó por filtración y se lava varias veces con agua. El sólido se colectó y se seca in vacuo para dar 2.85 g (98%) como un sólido beige. ^{1}H-RMN (CD_3OD) δ 1.32 (t, J=7.6, 3H), 2.50 (s,

3H), 2.88 (m, 2H), 7.25 (s, 1H), 7.68 (s, 1H). Espectro de masa: 239.26 $(MH)^+$.

7-Etil-3-metilindazol-5-carboxaldehído

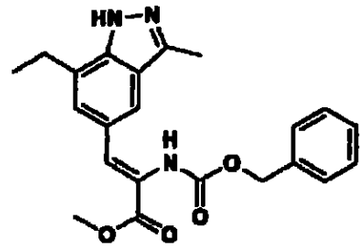


El 5-bromo-7-etil-3-metilindazol (2.85 g, 11.9 mmol) e hidruro de sodio (0.31 g, 1.1 equiv.) se pesaron en un matraz de fondo redondo secado a la flama que contienen una barra agitadora magnética. Bajo una atmósfera de nitrógeno a temperatura ambiente, el tetrahidrofurano seco (15 mL) se agregó. La mezcla se agitó a temperatura ambiente durante 15 min, tiempo durante lo cual se vuelve homogénea. La mezcla agitada se enfrió hasta -78°C y una solución de tert-butillitio en pentano (1.4M, 18.7 mL, 2.0 equiv) se agregó durante varios minutos. Después de 1 h a -78°C, la dimetilformamida (2.8 mL) se agregó lentamente y la mezcla se permitió que se entibiara a temperatura ambiente durante la noche. La solución se enfrió hasta 0°C y se trató cuidadosamente con ácido clorhídrico 1N (30 mL). Después de algunos minutos, el bicarbonato de sodio sólido se agregó hasta que se alcanza un pH de 9-10. Las dos capas se separaron y la fase acuosa se lava dos veces con acetato de

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etilo. Las capas orgánicas combinadas se lavaron con agua (2x), salmuera (2x), se secaron sobre sulfato de sodio, y se concentraron. La cromatografía de columna dio 1.5 g (67%) de material puro. CL/EM: tR = 1.15 min, 189.12 $(MH)^+$.

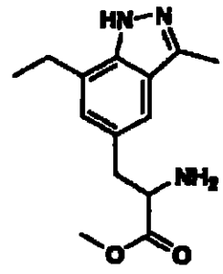
Éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-etil-3-metil-1H-indazol-5-il)-acrílico



Una solución agitada de éster de trimetil N-benciloxicarbonil-α-fosfonoglicina (3.17 g, 9.57 mmol, 1.2 equiv.) en tetrahidrofurano (15 mL) a temperatura ambiente se trató con tetrametilguanidina (1.1 mL, 1.1 equiv.). Después de 10 min, el 7-etil-3-metilindazol-5-carboxaldehído (1.5 g, 7.98 mmol) se agregó. Después de agitar a temperatura ambiente durante 3 días, el solvente se evaporó y el residuo se purificó por cromatografía instantánea en gel de sílice para dar 2.5 g (80%) del producto. CL/EM: tR = 1.61 min, 394.16 $(MH)^+$.

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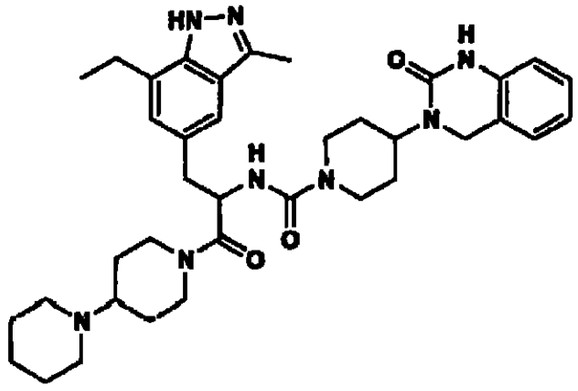
Éster de metilo del ácido (±)-2-amino-3-(7-etil-3-metil-1H-indazol-5-il)-propiónico



El éster de metilo del ácido 2-benciloxicarbonilamino-3-(7-etil-3-metil-1H-indazol-5-il)-acrílico (1.0 g, 2.54 mmol) en metanol (15 mL) se mojó con nitrógeno, y se trató con paladio en carbón vegetal (10%, 100 mg). El matraz se mojó con hidrógeno y se dejo agitar bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró. La cromatografía de columna dio 0.6 g del material deseado. ^{1}H-RMN (CD_3OD) δ 1.32 (m, 3H), 2.50 (s, 3H), 2.88 (dd, J=7.3, 7.6, 1H), 2.89 (dd, J=7.6, 7.6, 1H), 3.02 (dd, J=6.4, 7.0, 1H), 3.11 (dd, J=7.6, 5.8, 1H), 3.35 (s, 1H), 3.65 (m, 3H), 7.00 (s, 1H), 7.33 (s, 1H). Espectro de masa: 262.24 $(MH)^+$.

Ejemplo 207

[2-[1,4']bipiperidinil-1'-il-1(7-etil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

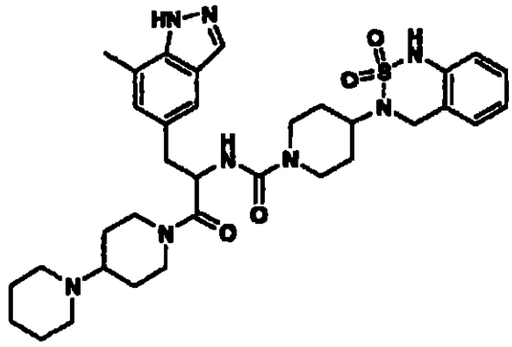


Preparado como se describe arriba por el Ejemplo 203 a partir del éster de metilo del ácido (±)-2-amino-3-(7-etil-3-metil-1H-indazol-5-il)-propiónico. ^{1}H-RMN (CD_3OD) δ 1.35 (m, 3H), 1.85-2.20 (m, 4H), 2.50 (s, 1H), 2.70 (m, 2H), 2.85 (s, 3H), 2.88-3.25 (m, 7H), 3.35 (s, 1H), 3.47 (dd, J=7.3, 7.3, 1H), 4.00-4.40 (m, 7H), 4.70 (m, 1H), 5.00 (m, 3H), 6.79 (d, J=7.6, 1H), 6.93 (dd, J=7.3, 7.3, 1H), 7.10 (m, 1H), 7.15 J=7.3, 7.6, 1H), 7.45 (m, 1H). Espectro de masa: 655.50 $(MH)^+$.

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Ejemplo 208

[2-[1,4']bipiperidinil-1'-il-1(7-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico

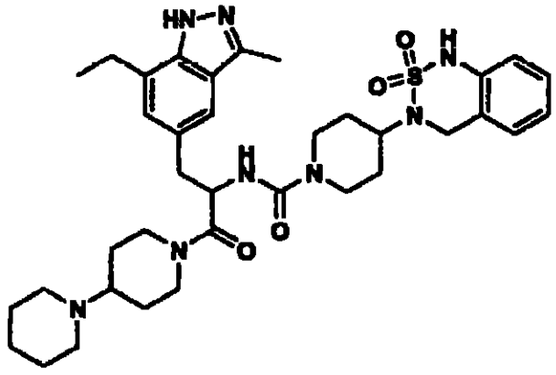


Preparado como se describe arriba por el Ejemplo 203 a partir de 3-piperidin-4-il-3,4-dihidro-1H-benzo[1,2,6]tiadiazina-2,2-dióxido: ^{1}H-RMN (CD_3OD) δ 1.20-2.10 (m, 12H), 2.20-2.60 (m, 6H), 2.90 (m, 6H), 3.78-4.11 (m, 4H), 4.60 (s, 3H), 4.90 (m, 1H), 6.70 (d, J=8.1, 1H), 6.79 (dd, J=7.67, 7.3, 1H), 7.44 (s, 1H), 7.10 (m, 1H), 7.13 (m, 3H), 8.03 (s, 1H). Espectro de masa: 663.60 $(MH)^+$.

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Ejemplo 209

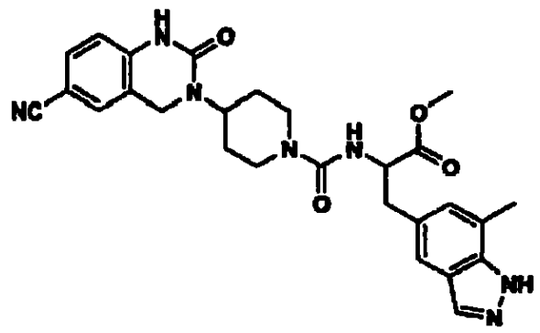
[2-[1,4']bipiperidinil-1'-il-1(7-etil-3-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico



Preparado como se describe arriba por el Ejemplo 203 a partir de 3-piperidin-4-il-3,4-dihidro-1H-benzo[1,2,6]tiadiazina-2,2-dióxido: ^{1}H-RMN (CD_3OD) δ 1.35 (m, 3H), 1.42-2.05 (m, 10H), 2.40 (m, 3H), 2.55 (s, 3H), 2.67-3.12 (m, 7H), 3.85 (m, 1H), 3.97 (s, 1H), 4.03 (m, 3H), 4.65 (m, 4H), 4.95 (dd, J=4.9, 5.8, 1H), 6.73 (d, J=7.9, 1H), 6.98 (dd, J=7.3, 6.4, 1H), 7.20 (m, 2H), 7.88 (s, 1H). Espectro de masa: 691.51 $(MH)^+$.

Ejemplo 210

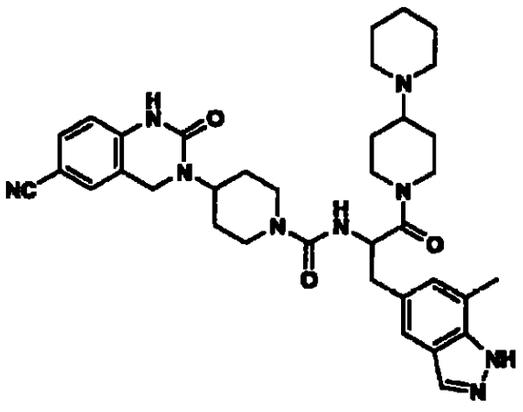
Éster de metilo del ácido (±)-2-[4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-3-(7-metil-1H-indazol-5-il)-propiónico



Preparado como se describe arriba por el éster de metilo del ácido 3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico: CL/EM: tR = 1.34 min, 516.40 $(MH)^+$.

Ejemplo 211

{2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il-metil)-2-oxo-etil}-amida del ácido (±)-4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

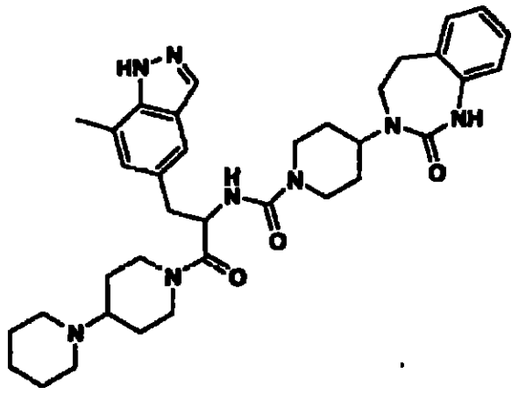


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Preparado como se describe arriba por el Ejemplo 203 a partir de 2-oxo-3-piperidin-4-il-1,2,3,4-tetrahidro-quinazolin-6-carbonitrilo: ^{1}H-RMN (CD_3OD) δ 1.80 (m, 12H), 2.40 (m, 4H), 2.60 (s, 3H), 2.70-3.20 (m, 10H), 4.00-4.30 (m, 6H), 5.00 (m, 1H), 5.50 (s, 2H), 6.90 (d, J=7.8, 1H), 7.21 (s, 1H), 7.50 (m, 4H), 8.05 (s, 1H). Espectro de masa: 652.64 $(MH)^+$.

Ejemplo 212

{2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-2-oxo-1,2,4,5-tetrahidro-benzo[d][1,3]diazepin-3-il-1-carboxílico

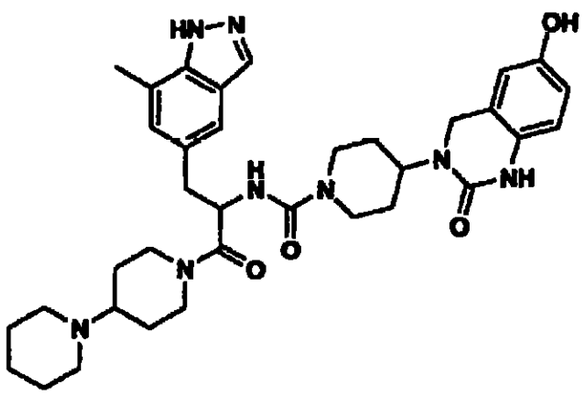


Preparado como se describe arriba por el Ejemplo 203 a partir de 3-piperidin-4-il-1,3,4,5-tetrahidro-benzo[d][1,3]diazepin-2-ona: ^{1}H-RMN (CD_3OD) δ 1.40-2.00 (m, 12H), 2.30-2.60 (m, 8H), 2.70-3.20 (m, 10H), 3.70 (m, 2H), 3.60 (d, J=9.5, 1H), 4.00-4.30 (m, 4H), 4.70 (m, 1H), 5.00 (m, 1H), 6.90 (m, 2H), 7.10 (m, 3H), 7.20 (s, 1H), 7.50 (s, 1H), 8.05 (s, 1H). Espectro de masa: 652.64 $(MH)^+$.

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Ejemplo 213

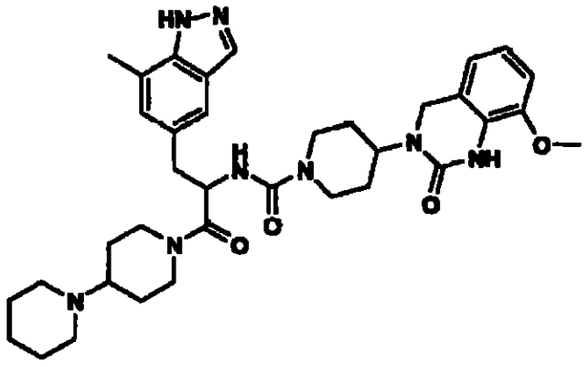
{2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-hidroxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparado como se describe arriba por el Ejemplo 203 a partir de 6-hidroxi-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona: CL/EM: tR = 1.24 min, 643.62 $(MH)^+$.

Ejemplo 214

{2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-metoxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



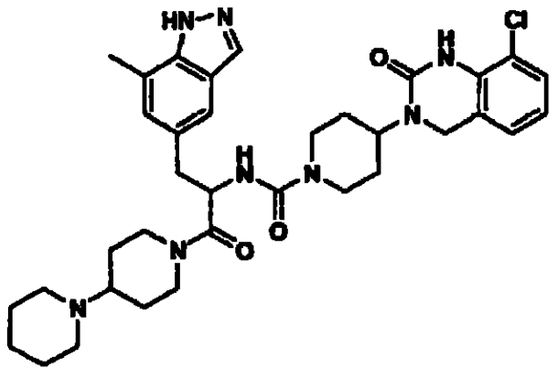
Preparado como se describe arriba por el Ejemplo 203 a

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partir de 8-metoxi-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona: ^{1}H-RMN (CD_3OD) δ 1.40-2.00 (m, 12H), 2.40 (m, 2H), 2.50 (s, 3H), 2.80 (m, 3H), 3.00-3.20 (m, 3H), 3.50 (m, 2H), 4.00-4.60 (m, 6H), 5.00 (m, 2H), 6.70 (dd, J=8.5, 10.1, 1H), 6.85 (m, 2H), 7.10 (m, 1H), 7.20 (s, 1H), 7.47 (s, 1H). Espectro de masa: 657.41 $(MH)^+$.

Ejemplo 215

{2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-cloro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

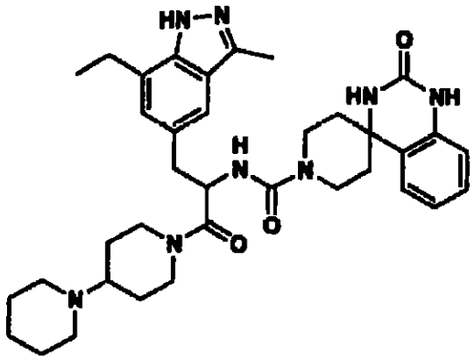


Preparado como se describe arriba por el Ejemplo 203 a partir de 2-cloro-3-piperidin-4-il-3,4-dihidro-1H-quinazolin-2-ona: ^{1}H-RMN (CD_3OD) δ 1.40-2.00 (m, 14H), 2.30-2.60 (m, 8H), 2.80 (m, 4H), 3.50 (m, 3H), 3.98 (s, 1H), 4.10 (m, 4H), 4.40 (m, 2H), 4.60 (m, 1H), 4.95 (m, 1H), 6.95 (dd, J=7.9, 7.9, 1H), 7.10 (m, 1H), 7.26 (dd, J=6.7, 7.6, 1H), 7.47 (m, 1H), 8.04 (s, 1H). Espectro de masa: 661.27 $(MH)^+$.

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Ejemplo 216

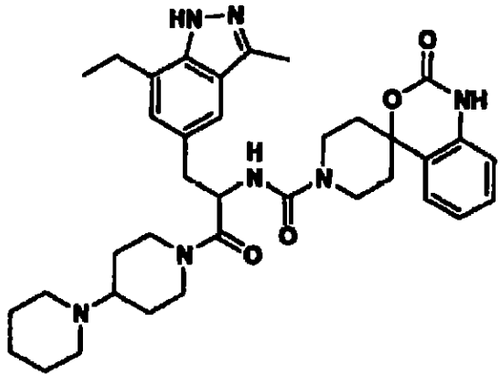
(±)-N-(3-(7-etil-3-metil-1H-indazol-5-il)-1-oxo-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolin)-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: CL/EM: tR = 1.51 min, 641.63 $(MH)^+$.

Ejemplo 217

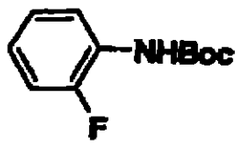
(±)-N-(3-(7-etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida



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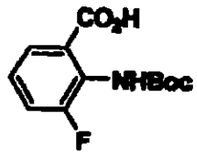
Preparado como se describe arriba por el Ejemplo 203: CL/EM: tR = 1.48 min, 642.61 $(MH)^+$.

tert-Butil 2-fluorofenilcarbamato



A una solución de di-tert-butildicarbonato (45.2 g, 207 mmol, 1.0 equiv.) en tetrahidrofurano (210 mL) a temperatura ambiente se agregó 2-fluoroanilina (20.0 mL, 207 mmol). La reacción se calentó a reflujo y se mantiene así durante 6h. Se enfrió, se concentró, se disuelve en pentano, se lava con ácido cítrico al 5%, luego bisulfato de potasio 1 M (2x), luego agua, luego hidróxido de potasio al 20%, luego salmuera, se seca sobre sulfato de magnesio, y se concentró para dar 48.0 g (cuantitativo) como un aceite ámbar que se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.52 (s, 9H), 6.68 (bs, 6.85-7.20 (m, 3H), 8.07 (dd, J=8.1, 8.1, 1H). Espectro de masa: 234.18 $(MNa)^+$.

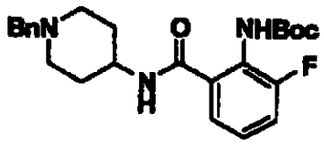
Ácido 2-(tert-butoxicarbonilamino)-3-fluoro-benzoico



A una solución de 2-fluorofenilcarbamato de tert-butilo

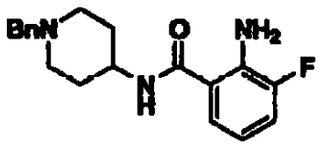
(44.0 g, 208 mmol) en tetrahidrofurano (660 mL) a -78°C se le agregó tert-butillitio en pentano (1.7 M, 306 mL, 2.5 equivalentes) gota a gota. Después de que la adición se completó, la reacción se agitó a -78°C durante 30 min. La solución se permitió que alcanzara gradualmente -20°C antes de volverse a enfriar hasta -78°C y se transfiere por medio de una cánula a una mezcla espesa de dióxido de carbono (exceso) y tetrahidrofurano (500 mL). La solución se permitió lentamente entibiarse a temperatura ambiente. La mezcla de reacción se concentró para remover la mayoría del tetrahidrofurano, y se vacía en un embudo separador que contienen agua y éter de dietilo. Las capas se separaron, y la acuosa se extrajo con éter de dietilo dos veces más. Los etéreos se descartaron. La acuosa se hizo ácida con ácido cítrico al 5%, se extrajo con éter de dietilo (3x). El etéreo se secó sobre sulfato de magnesio, y se concentró para dar un sólido amarillo ligero el cual se recristalizó de tolueno caliente para dar 37.1 g (70%) como un sólido amarillo tenue ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.50 (s, 9H), 6.25 (bs, 1H), 7.18 (ddd, J=7.9, 7.9, 4.9, 1H), 7.33 (dd, J=9.5, 9.2, 1H), 7.79 (d, J=7.9, 1H), 7.94 (s, 1H). Espectro de masa: 278.21 $(MNa)^+$.

2-(1-bencilpiperidin-4-ilcarbamnoil)-6-fluorofenilcarbamato de tert-butilo



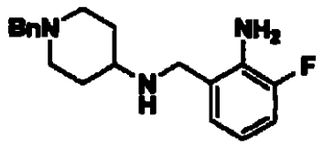
A una solución de ácido 2-(tert-butoxicarbonilamino)-3-fluoro-benzoico (37.1 g, 145 mmol) 4-amino-1-bencilpiperidina (35.6 mL, 1.20 equiv.), 1-hidroxibenzotriazol (21.6 g, 1.1 equiv.), y trietilamina (44.1 g, 3.0 equiv.) en acetato de etilo (450 mL) se le agregó clorohidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (30.7 g, 1.1 equiv.) en una porción. Inicialmente, todo dentro de un solución, pero un precipitado se formó muy rápidamente. La reacción se equipó con un condensador de reflujo y se calentó a reflujo durante 5 h. La reacción se diluyó con acetato de etilo, se lava con agua (2x), luego hidróxido de sodio 1N (2x), luego salmuera, se seca sobre sulfato de magnesio, y se concentró para dar 67.0 g (cuantitativo) como un sólido blanco el cual se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.48 (s, 9H), 1.55 (m, 2H), 1.99 (bd, J=11.0, 2H), 2.17 (dd, J=11.0, 11.0, 2H), 2.84 (bd, J=11.3, 2H), 3.51 (s, 2H), 3.94 (m, 1H), 6.13 (bd, J=7.6, 1H), 7.10-7.28 (m, 4H), 7.31 (m, 4H), 7.59 (s, 1H). Espectro de masa: 428.41 $(MH)^+$.

2-Amino-N-(1-bencilpiperidin-4-il)-3-fluorobenazamida



A una solución de 2-(1-bencilpiperidin-4-ilcarbamoil)-6-fluorofenilcarbamato de tert-butilo (67.0 g, 157 mmol) en diclorometano (700 mL) a 0°C se le agregó ácido trifluoroacético (100 mL). El baño de hielo se removió y la reacción se agitó a temperatura ambiente durante la noche. La reacción se concentró y se divide entre acetato de etilo y bicarbonato de sodio saturado. La acuosa se extrajo con acetato de etilo (2x), la cual se lavó con agua (3x), luego salmuera, se seca sobre sulfato de magnesio, y se concentró para dar 47.6 g (93%) como un sólido blanco el cual se usó sin purificación. Espectro de masa: 328.33 $(MH)^+$.

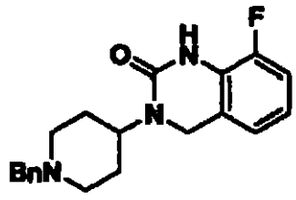
N-(2-Amino-3-fluorobencil)-1-bencilpiperidin-4-amina



A una suspensión a reflujo de hidruro de litio aluminio (16.1 g, 424 mmol, 3.50 equiv.) en dioxano (800 mL) se le agregó una solución de 2-amino-N-(1-bencilpiperidin-4-il)-3-fluorobenzamida (39.7 g, 121 mmol) en dioxano (250 mL) a una relación tal que la evolución del gas se limita a un flujo

seguro. Una vez completada la adición, la suspensión resultante se calentó a reflujo durante 4 h. La reacción se enfrió hasta 0°C, y se apaga por la adición cuidadosa de hidróxido de potasio al 20%. Una vez que se forma un precipitado que se puede filtrar, blanco, el sólido se filtró a través un embudo sinterizado de vidrio grueso, y el eluyente se concentra para dar 36.3 g (96%) como un aceite amarillo ligero el cual se usó sin purificación. Espectro de masa: 314.29 $(MH)^+$.

3-(1-bencilpiperidin-4-il)-8-fluoro-3,4-dihidroquinazolin-2(1H)-ona

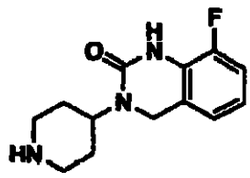


A una solución de N-(2-amino-3-fluorobencil)-1-bencilpiperidin-4-amina (36.3 g, 116 mmol) en tetrahidrofurano (600 mL) a temperatura ambiente se agregó diimidazol carbonilo (20.7 g, 10 equiv.) en una porción. La reacción se agitó a temperatura ambiente durante 3 h, se calentó a reflujo durante 30 min, y se concentró. El sólido resultante se disolvió en 1:1 éter de dietilo/acetato de etilo, se lava con agua (3x), luego salmuera, se seca sobre sulfato de magnesio, y se concentró para dar el producto

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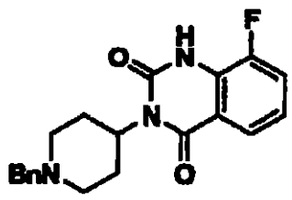
crudo como un sólido amarillo, húmedo. El sólido se trituró con éter de dietilo y se filtra para dar 30.0 g (76%) como un polvo blanco. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.68 (m, 2H), 1.86 (dddd, J=11.9, 11.9, 11.9, 3.4, 2H), 2.14 (dd, J=11.6, 10.1, 2H), 2.98 (d, J=11.6, 2H), 3.51 (s, 2H), 4.34-4.44 (m, 3H), 6.71 (bs, 1H), 6.79-6.89 (m, 2H), 6.94 (dd, J=9.2, 9.2, 1H), 7.21-7.34 (m, 5H). Espectro de masa: 340.30 $(MH)^+$.

8-Fluoro-3,4-dihidro-3-(piperidin-4-il)quinazolin-2(1H)-ona



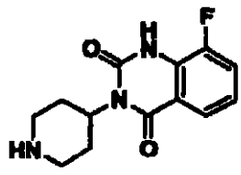
Un matraz de 250 mL se cargó con 3-(1-bencilpiperidin-4-il)-8-fluoro-3,4-dihidroquinazolin-2(1H)-ona (1.40 g, 4.12 mmol) y metanol (25.0 mL). La suspensión se calentó con una pistola de calor para ayudar en la disolución. El matraz se mojó con nitrógeno, se trató con paladio en carbón vegetal (141 mg, 0.032 equiv.), se moja con nitrógeno, luego hidrógeno, y se agitó vigorosamente bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través celite, y se concentró para dar 0.99g (97%) como un sólido blanco el cual se usó sin purificación. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.71 (m, 4H), 2.75 2H), 3.16 (m, 2H), 4.38 (s, 2H), 4.46 (m, 1H), 6.77 (bs, 1H), 6.81-6.89 (m, 2H), 6.95 (m, 1H). Espectro de masa: 250.22 $(MH)^+$.

3-(1-bencilpiperidin-4-il)-8-fluoroquinazolina-2,4(1H,3H)-diona



A una solución de 2-amino-N-(1-bencilpiperidin-4-il)-3-fluorobenzamida (750 mg, 2.29 mmol) en diclorometano (30.0 mL) a 0°C, se le agregó trifosgeno (227 mg, 0.33 equiv.) como una solución en diclorometano (5 mL). El baño de hielo se removió y la reacción se calentó a reflujo durante 6h. La reacción se concentró, se disuelve en acetato de etilo, se lava con bicarbonato de sodio saturado, luego agua, luego salmuera, se seca sobre sulfato de magnesio, y se concentró para dar 700 mg de un sólido blanco. El producto crudo se purificó por cromatografía instantánea para dar 205 mg (25%) como un sólido blanco. Espectro de masa: 354.13 $(MH)^+$.

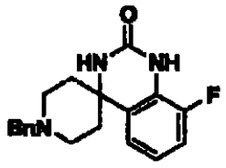
8-Fluoro-3-(piperidin-4-il)quinazolina-2,4(1H,3H)-diona



Un matraz que contienen una solución de 3-(1-bencilpiperidin-4-il)-8-fluoroquinazolin-2,4(1H,3H)-diona (75.0 mg, 0.21 mmol) y paladio en carbón vegetal (8.00 mg,

0.035 equiv) en metanol (3.00 mL) se mojó primero con nitrógeno, luego hidrógeno. La reacción se agitó bajo una atmósfera de hidrógeno durante la noche. La reacción se mojó con nitrógeno, se filtró a través de celite, y se concentró para dar 53 mg (95%) como un sólido blanco el cual se usó sin purificación. Espectro de masa: 264.25 $(MH)^+$.

8'-Fluoro-2',3'-dihidro-2'-oxoespiro-(1-fenilmetilpiperidina)-4,4'-quinazolina

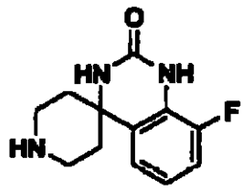


Un matraz de 3 cuellos de 500 mL se cargó con ácido polifosfónico (110 mL) y se equipa con un agitador de domo, una entrada de nitrógeno, y un burbujeador. El matraz se mojó con nitrógeno y se calentó hasta 105°C en un baño de aceite. A esto se le agregó 1-bencil-4-piperidona (21.0 mL, 115 mmol). A esto se le agregó N-(2-fluorofenil)urea (21.3 g, 1.2 equiv) en porciones muy pequeñas durante 2h. La reacción se calentó hasta 160°C con agitación vigorosa. Después de 2h, la reacción se apagó al vaciar sobre hielo molido y neutralizar con hidróxido de potasio al 20%. La mezcla de reacción se extrajo con diclorometano, se lava con agua, luego salmuera, se seca sobre sulfato de magnesio, y se concentró. El lote completo se purificó por CLAR preparativa (~130 inyecciones)

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para dar un producto mucho más puro. El producto se volvió a purificar por cromatografía instantánea para dar un sólido el cual se trituró con éter de dietilo y se filtró para dar 275 mg (0.7%) como un sólido blanco. ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.91 (dd, J=13.7, 2.1, 2H), 2.10 (ddd, J=13.1, 13.1, 4.3, 2H), 2.27 (ddd, J=12.5, 12.5, 2.1, 2H), 2.86 (m, 2H), 3.57 (s, 2H), 5.40 (bs, 1H), 6.90 (bs, 1H), 6.90-7.05 (m, 3H), 7.27 (m, 1H), 7.32 (m, 4H). Espectro de masa: 326.13 $(MH)^+$.

8'-Fluoro-2',3'-dihidro-2'-oxoespiro-piperidin-4,4'-quinazolina

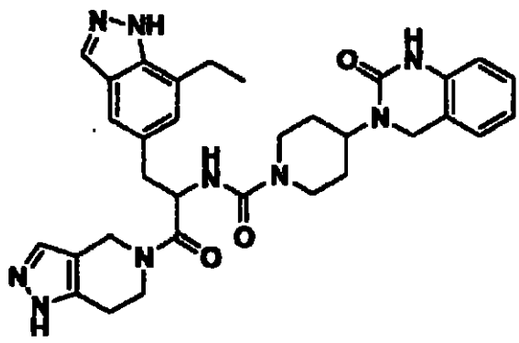


A una solución de 8'-fluoro-2',3'-dihidro-2'-oxoespiro-(1-fenilmetilpiperidin)-4,4'-quinazolina (250 mg, 0.77 mmol) en metanol (4 mL) y diclorometano (4 mL) se agregó paladio en carbón vegetal (30.0 mg, 0.037 equiv.). La reacción se mojó con hidrógeno, y se agitó bajo una atmósfera de hidrógeno durante la noche. El globo se removió, la reacción se moja con nitrógeno, se filtró a través celite, se lava con metanol adicional, y se concentró para dar 158 mg (87%) como un sólido blanco el cual se usó sin purificación. 1H-RMN ($CDCl_3/CD_3OD$, 500 MHz) δ 1.87 (d, J=12.8, 2H), 2.15 (dd, J=14.0, 14.0, 5.5, 2H), 3.10 (m, 4H), 6.84 (m, 2H), 6.93 (d,

J=7.0, 1H). Espectro de masa: 236.11 $(MH)^+$.

Ejemplo 218

(±)-N-(3-(7-etil-1H-indazol-5-il)-1-(6,7-dihidro-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida

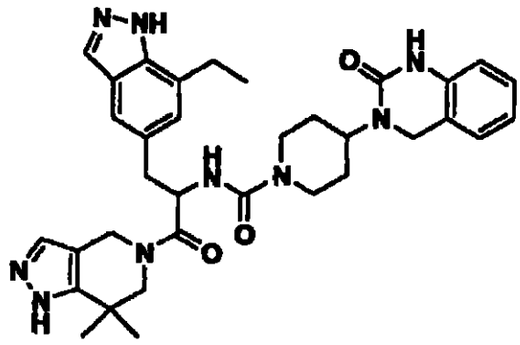


Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.24 (m, 2H), 1.55-2.07 (m, 5H), 2.57 (m, 1H), 2.82 (m, 4H), 3.08 (m, 2H), 3.30 (m, 3H), 3.35 (m, 5H), 3.48 (m, 3H), 3.65 (m, 1H), 4.14 (m, 2H), 4.27 (m, 2H), 4.33-4.57 (m, 2H), 5.06 (dd, J=6.7, 6.7, 1H), 5.22 (d, J=1.8, 2H), 6.78 (d, J=7.6, 1H), 6.93 (m, 1H), 7.00-7.18 (m, 3.5 H), 7.37 (d, J=9.8, 1H), 7.46 (s, 0.5H), 7.91 (dd, J=10.1, 1.8, 1H). Espectro de masa: 596.43 $(MH)^+$.

777 751

Ejemplo 219

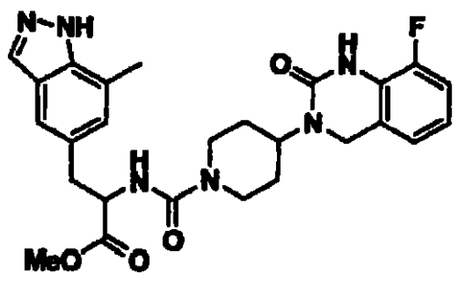
(±)-N-(3-(7-etil-1H-indazol-5il)-1-(6,7-dihidro-7,7-dimetil-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203 ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.11 (m, 3H), 1.50-1.80 (m, 4H), 2.87 (m, 4H), 3.10 (m, 2H), 3.32 (m, 9H), 3.48 (m, 4H), 4.00-4.45 (m, 6H), 5.05-5.25 (m, 2H), 6.77 (d, J=6.1, 1H), 6.93 (m, 1H), 7.13 (m, 3H), 7.30-7.60 (m, 2H), 7.95 (m, 1H). Espectro de masa: 624.49 $(MH)^+$.

Ejemplo 220

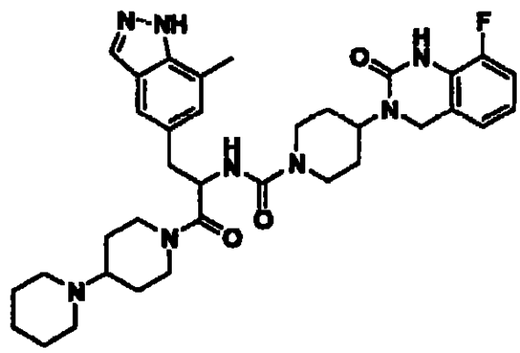
2-(4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-indazol-5-il)propanoato de (±)-metilo



Preparado como se describe arriba por éster de metilo del ácido 3-(3-ciano-1H-indol-5-il)-2-([4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]amino)-propiónico: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.53-1.68 (m, 4H), 2.48 (s, 3H), 2.82 (m, 2H), 3.05 (m, 6H), 3.09 (dd, J_{AB}=13.7, 6.1, 1H), 3.14 (dd, J_{AB}=14.0, 6.1, 1H), 3.35 (bs, 1H), 3.68 (s, 3H), 3.88-4.02 (m, 2H), 4.22 (d, J_{AB}=15.6, 1H), 4.25 (d, J_{AB}=15.3, 1H), 4.44 (m, 1H), 4.71 (dd, J=6.1, 6.1, 1H), 6.78 (d, J=7.3, 1H), 6.84 (ddd, J=7.6, 7.6, 4.9, 1H), 6.88-6.95 (m, 2H), 7.28 (s, 1H), 7.91 (s, 1H). Espectro de masa: 509.25 $(MH)^+$.

Ejemplo 221

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3-(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)propan-2-il)piperidin-1-carboxamida

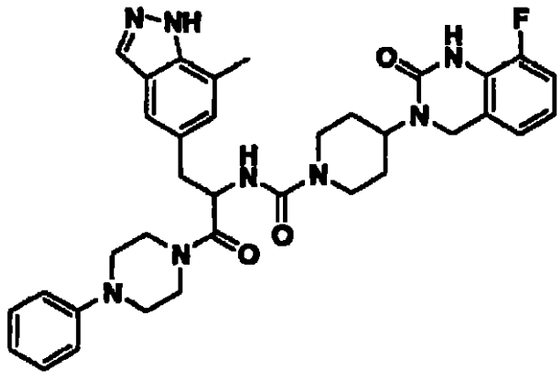


Preparado como se describe arriba por el Ejemplo 203 (CD_3OD, 500 MHz) δ -0.25 (m, 1H), 0.82 (m, 1H), 1.25-2.10 (m, 13H), 2.20-2.63 (m, 6H), 2.68-2.98 (m, 4H), 3.00-3.22 (m, 3H), 3.31 (m, 2H), 3.44 (bs, 1H), 4.00-4.50 (m, 6H), 4.64 (m,

1H), 4.96 (m, 1H), 6.85-7.05 (m, 3H), 7.08 (s, 0.4H), 7.20 (s, 0.6H), 7.46 (d, J=7.0, 1H), 7.99 (s, 0.4H), 8.05 (d, J=2.4, 0.6H). Espectro de masa: 645.58 $(MH)^+$.

Ejemplo 222

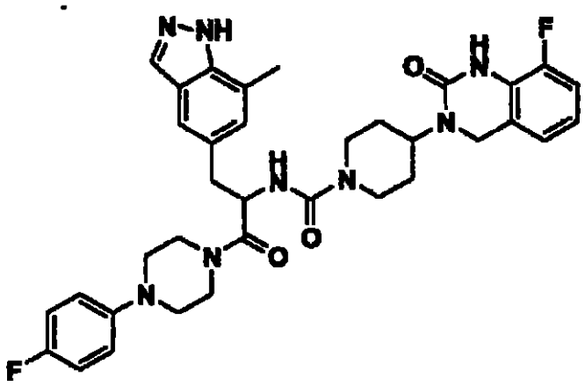
(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-fenilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.73 (m, 4H), 2.49 (m, 4H), 2.80-3.26 (m, 7H), 3.43 (m, 2H), 3.65-3.95 (m, 3H), 4.14 (dd, J=21.7, 14.3, 2H), 4.32 (s, 2H), 4.51 (m, 1H), 5.15 (dd, J=7.9, 6.4, 1H), 5.90 (bs, 1H), 6.80 (d, J=7.3, 1H), 6.83-7.01 (m, 4H), 7.06 (dd, J=7.6, 7.3, 1H), 7.10 (s, 1H), 7.26-7.33 (m, 2H), 7.44 (s, 1H), 7.87 (s, 1H), 8.06 (s, 1H). Espectro de masa: 639.36 $(MH)^+$.

Ejemplo 223

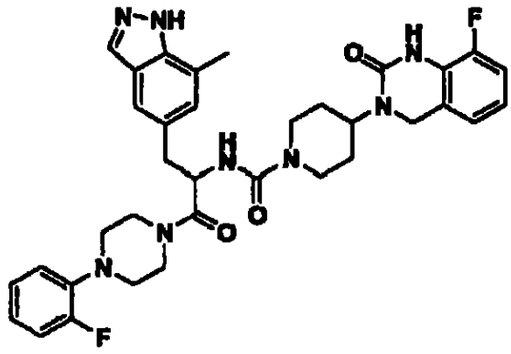
(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(4-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.73 (m, 4H), 2.26 (dd, J=7.9, 7.6, 1H), 2.49 (s, 3H), 2.75-3.05 (m, 4H), 3.09 (m, 2H), 3.19-3.45 (m, 3H), 3.63 (m, 1H9, 3.78 (m, 2H), 4.13 (dd, J=16.5, 15.3, 2H), 4.32 (s, 2H), 4.50 (m, 1H), 5.15 (dd, J=8.2, 6.1, 1H), 5.85 (bs, 1H), 6.70-6.84 (m, 3H), 6.85-7.02 (m, 5H), 7.09 (s, 1H), 7.43 (s, 1H), 7.78 (s, 1H), 8.06 (s, 1H). Espectro de masa: 657.35 $(MH)^+$.

Ejemplo 224

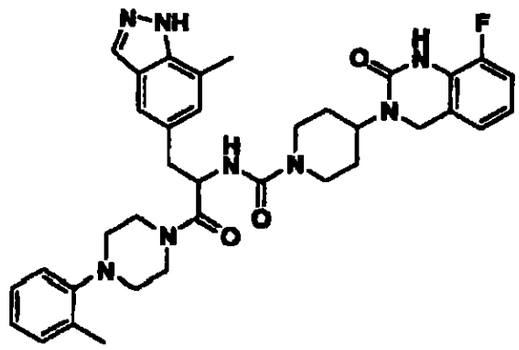
(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(2-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.62-1.78 (m, 4H), 2.24 (dd, J=7.9, 8.2, 1H), 2.50 (s, 3H), 2.70-2.85 (m, 2H), 2.85-2.96 (m, 2H), 2.00 (m, 1H), 3.08 (dd, J_{AB}=13.1, 8.6, 1H), 3.12 (m, 1H), 3.30 (m, 1H), 3.57 (m, 1H), 3.73 (m, 2H), 4.13 (dd, J=19.8, 15.0, 2H), 4.33 (s, 2H), 4.53 (m, 1H), 5.18 (dd, J=8.2, 5.8, 1H), 5.82 (bs, 1H), 6.58 (dd, J=8.2, 8.2, 1H), 6.81 (d, J=7.6, 1H), 6.85-7.05 (m, 5H), 7.09 (s, 1H), 7.44 (s, 1H), 7.58 (s, 1H), 8.05 (s, 1H). Espectro de masa: 657.37 $(MH)^+$.

Ejemplo 225

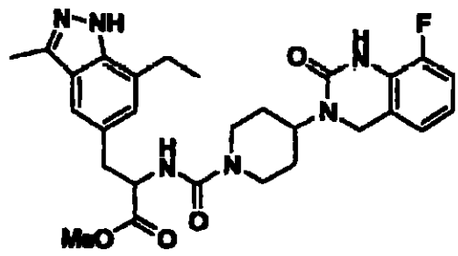
(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-o-tolilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN ($CDCl_3$, 500 MHz) δ 1.60-1.79 (m, 4H), 2.03 (dd, J=8.5, 8.2, 1H), 2.22 (s, 3H), 2.49 (s, 3H), 2.54 (dd, J=8.6, 8.5, 1H), 2.65 (m, 1H), 2.81 (m, 1H), 2.85-2.97 (m, 2H), 3.05-3.22 (m, 3H), 3.38 (m, 1H), 3.50-3.65 (m, 2H), 3.83 (m, 1H), 4.15 (dd, J=15.9, 15.3, 2H), 4.31 (s, 2H), 4.53 (m, 1H), 5.19 (dd, J=7.9, 5.8, 1H), 5.84 (bs, 1H), 6.54 (d, J=7.6, 1H), 6.81 (d, J=7.6, 1H), 6.89 (ddd, J=7.6, 7.6, 5.2, 1H), 6.96 (m, 2H), 7.00-7.23 (m, 4H), 7.39 (s, 1H), 7.43 (s, 1H), 8.04 (s, 1H). Espectro de masa: 653.38 $(MH)^+$.

Ejemplo 226

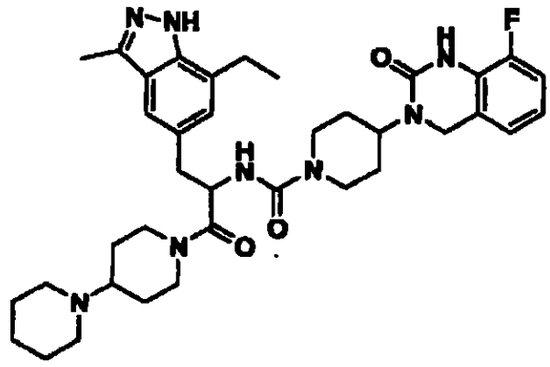
2-(4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-etil-3-metil-1H-indazol-5-il)propanoato de (±)-metilo



Preparado como se describe arriba por el éster de metilo del ácido 3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico: ^{1}H-RMN (CD_3OD, 500 MHz) δ 1.33 (m, 3H), 1.39-1.72 (m, 4H), 2.70-2.95 (m, 3H), 3.06 (m, 1H), 3.25 (m, 1H), 3.70 (m, 3H), 3.95-4.30 (m 4H), 4.38 (m, 1H9, 4.57 (m, 1H), 6.80-7.05 (m, 3H), 7.08 (s, 1H), 7.38 (s, 1H). Espectro de masa: 537.47 $(MH)^+$.

Ejemplo 227

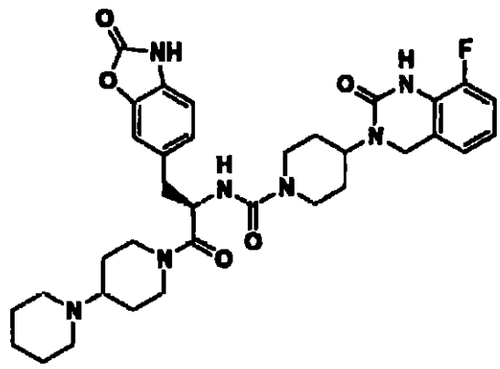
(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD, 500 MHz) δ -0.36 (m, 1H9, 0.70 (m, 1H), 1.21 (bd, J=11.9, 1H), 1.28-2.00 (m, 19H), 2.31 (dd, J=11.6, 11.3, 1H), 2.40 (dd, J=13.1, 11.6, 1H), 2.79-3.16 (m, 7H), 3.72 (m, 1H), 3.85-4.03 (m, 1H), 4.10-4.48 (m, 5H), 4.53 (bd, J=11.0, 1H), 5.05 (m, 1H), 6.85-7.03 (m, 3H), 7.08 (s, 0.2H), 7.18 (s, 0.8H), 7.37 (s, 1H). Espectro de masa: 673.42 $(MH)^+$.

Ejemplo 228

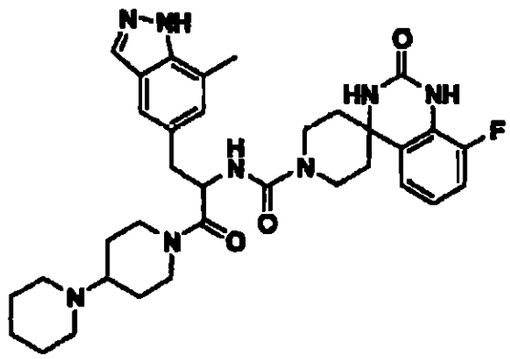
(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD, 500 MHz) δ 0.71 (m, 1H), 1.26 (m, 1H), 1.40-2.15 (m, 13H), 2.50-3.29 (m, 9H), 3.32-3.64 (m, 3H), 4.14 (d, J_{AB}=12.8, 1H), 4.17 (d, J_{AB}=11.6, 1H), 4.32-4.45 (m, 3H), 4.68 (bd, J=13.4, 1H), 4.92 (m, 1H), 6.87-7.22 (m, 6H). Espectro de masa: 648.47 $(MH)^+$.

Ejemplo 229

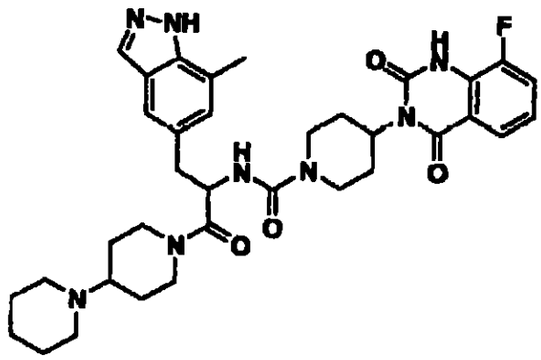
(±)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-piperidin-1-il)piperidin-1-il)propan-2-il)-8'-fluoro-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD, 500 MHz) δ -0.23 (m, 1H), 0.85 (m, 1H), 1.20-2.10 (m, 22H), 2.25-2.55 (m, 7H), 2.58 (s, 3H), 2.74 (d, J=11.3, 1H), 2.94 (dd, J=12.5, 12.2, 2H), 3.00-3.20 (m, 5H), 3.40-3.65 (m, 2H), 3.80-4.15 (m, 4H), 4.55-4.73 (m, 2H), 4.96 (dd, J=7.9, 7.6, 1H), 5.01 (dd, J=10.4, 5.8, 1H), 6.65-7.15 (m, 5H), 7.21 (s, 1H), 7.47 (s, 1H), 7.96 (m, 1H), 8.04 (s, 1H). Espectro de masa: 631.29 $(MH)^+$.

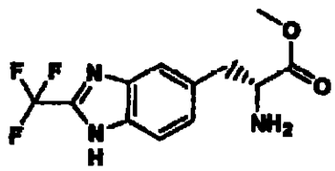
Ejemplo 230

(±)-4-(8-Fluoro-1,2-dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 203: ^{1}H-RMN (CD_3OD, 500 MHz) δ -0.26 (m, 1H), 0.81 (m, 1H), 1.20-2.10 (m, 11H), 2.20-2.80 (m, 9H), 2.90 (m, 3H), 3.10 (m, 3H), 3.34 (m, 1H), 3.44 (m, 1H), 4.06 (bd, J=13.4, 1H), 4.17 (d, J_{AB}=15.9, 1H), 4.22 (d, J_{AB}=13.1, 1H), 4.64 (dd, J=24.4, 13.1, 1H), 4.91-5.13 (m, 2H), 7.00-7.25 (m, 2H), 7.44 (m, 2H), 7.81 (m, 1H), 7.92-8.08 (m, 1H). Espectro de masa: 659.59 $(MH)^+$.

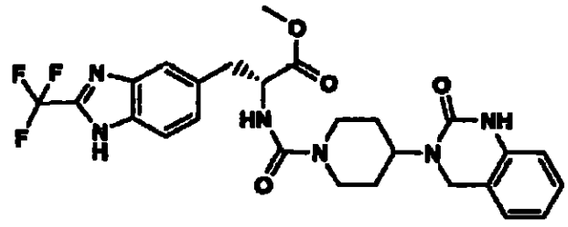
2-Amino-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo



Una mezcla del éster de metilo del ácido (R)-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico (500 mg, 1.20 mmol) y ácido trifluoroacético (6 mL) se

calentó a 80°C durante 16 h. La mezcla de reacción se vació en agua con hielo (75 mL), se neutralizó hasta pH 7 con bicarbonato de sodio saturado acuoso, y se extrajo con acetato de etilo (2 x 250 mL). Los extractos orgánicos se secaron sobre sulfato de sodio, se filtraron y evaporaron para dar el compuesto del título como la sal del ácido trifluoroacético (459 mg, 84 % de rendimiento). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.37 (bs, 7.35 (bs, 7.17 (d, J = 8.4 Hz, 1H), 4.70 (s, 2 H), 3.85 (dd, J = 8.4, 4.8 Hz, 1H), 3.77 (s, 3H), 3.30 (dd, J = 13.9, 4.8 Hz, 1H), 2.97 (dd, J = 13.5, 8.4 Hz, 1H). Espectro de masa: 288 $(MH)^+$.

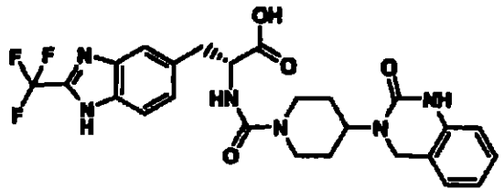
2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo



Una solución del 2-amino-3-(2-trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de amino éster (R)-metilo (230 mg, 0.51 mmol), diisopropiletilamina (262 mg, 2.03 mmol), y carbonato de disuccinimidilo (129 mg, 0.51 mmol) en una mezcla de cloruro de metileno/dimetilformamida (relación

15:1) se agitó a temperatura ambiente durante 30 min. A la solución se le agregó 4-(2-ceto-1-benzimidazolinil)piperidina y la mezcla de reacción se dejo agitar a temperatura ambiente durante 16 h. La mezcla de reacción se filtró para remover cualquier sólido y luego se purificó por cromatografía de columna instantánea (95:3:2 cloruro de metileno/metanol/trietilamina) para dar el compuesto del título (215 mg, 77 % de rendimiento) como un sólido color canela. ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 8.4 Hz, 1H), 7.39 (s, 1H), 7.21-7.16 (m, 1H), 7.05-6.94 (m, 3H), 6.70-6.68 2H), 5.11 (d, J = 7.3 Hz, 1H), 4.78 (dd, J = 12.1, 5.5 Hz, 1H), 4.42 (d, J = 4.4 Hz, 2H), 4.29 (d, J = 12.1 Hz, 1H9, 3.82-3.72 (m, 2H), 3.74 (s, 3H), 3.44 (dd, J = 13.9, 5.5 Hz, 1H), 3.22 (dd, J = 13.9, 5.5 Hz), 2.95-2.83 (m, 3H), 2.18-2.03 (m, 2H), 1.79-1.68 (m, 2H). Espectro de masa: 545 $(MH)^+$.

Ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico

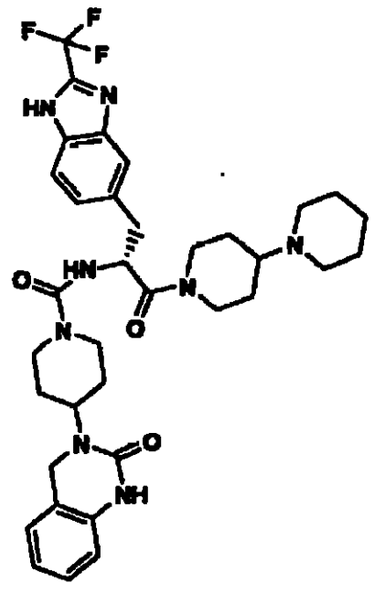


A una solución del éster de 2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-

metilo (220 mg, 0.40 mmol) en tetrahidrofurano y metanol (mezcla 1:1, 20 mL) a 0°C, se le agregó hidróxido de litio (36 mg, 1.51 mmol) en agua (10 mL). La mezcla se agitó a 0°C durante 2 h y luego se almacenó a -15°C durante 16 h. Los solventes orgánicos se evaporaron. La solución acuosa se extrajo con acetato de etilo mientras se ajusta el pH hasta 4 con HCl 1N (3 mL). Los extractos orgánicos se secaron sobre sulfato de sodio, se filtraron, y evaporaron para dar el compuesto del título (176 mg, 82% de rendimiento). CL/EM: tR = 2.01 min, 531 $(MH)^+$.

Ejemplo 231

N-((R)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)-1-oxo-1-(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida

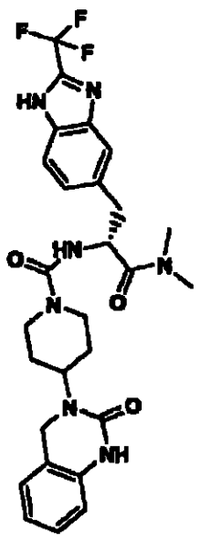


A una solución agitada del ácido (R)-2-(4-(1,2-dihidro-

2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-propanoico (33 mg, 0.06 mmol) y diisopropiletilamina (33 mg, 0.25 mmol) en cloruro de metileno (2 mL) se le agregó una solución de PyBOP (33 mg, 0.06 mmol) y 4-piperidinopiperidina (12 mg, 0.07 mmol) en cloruro de metileno (1mL). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se sometió a cromatografía de capa delgada preparativa para purificación (1:10 amoniaco 2M en metanol/cloruro de metileno) para dar el compuesto del título (4.6 mg, 12% de rendimiento). ^{1}H-RMN (CD_3OD, 500 MHz) δ 7.73-7.71 (m, 1H), 7.62 (bs, 1H), 7.39-7.36 (m, 1H), 7.19-7.11 (m, 2H), 6.96 (t, J = 7.2 Hz, 1 H), 6.81 (d, J = 7.9 Hz, 1H9, 5.06-5.02 (m, 1H), 4.67-4.58 (m, 1H), 4.49-4.40 (m, 1H), 4.38 (s, 1H), 4.33 (bs, 1H), 4.25-4.16 (m, 2H), 4.10-4.03 (m, 1H), 3.22-3.14 (m, 3H), 3.04-2.87 (m, 4H), 2.79-2.71 (m, 1H), 2.58-2.48 (m, 1H), 2.44-2.33 (m, 1H), 2.31-2.22 (m, 1H), 2.04-1.92 (m, 1H), 1.86-1.43 (m, 11H), 1.33-1.29 (m, 1H), 0.94-0.84 (m, 1H), -0.04- -0.12 (m, 1H). CL/EM: tR = 1.97 min, 681 $(MH)^+$.

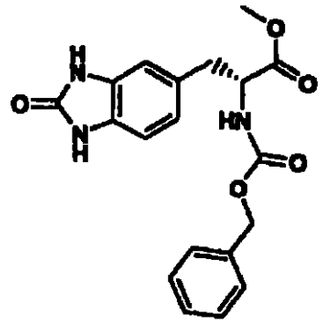
Ejemplo 232

N-((R)-1-(dimetilcarbamoil)-2-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida



Preparado como se describe arriba por el Ejemplo 231. ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.69-7.56 (m, 2H), 7.34 (d, J=7.7 Hz, 1H), 7.17-7.08 (m, 2H), 6.92 (t, J = 7.7 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 7.7 Hz, 1H), 5.02-4.97 (m, 1H9, 4.46-4.35 (m, 1H), 4.29 (s, 2H), 4.15 (d, J = 12.8 Hz, 1H), 3.26-3.11 (m, 5H), 2.87 (s, 6H), 1.86-1.68 (m, 2H), 1.66-1.59 (m, 2H). CL/EM: tR = 2.37 min, 558 $(MH)^+$.

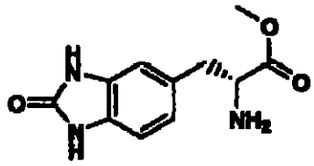
(R)-1-(metoxicarbonil)-2-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)etilcarbamato de bencilo



A una solución diluida de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(3,4-diamino-fenil)-propiónico (600 mg, 1.44 mmol) en tetrahidrofurano (125 mL) se le agregó trietilamina (320 mg, 3.17 mmol) seguido por 1,1'-carbonildiimidazol (280 mg, 1.73 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y luego se filtra para remover el sólido. El filtrado se evaporó y se sometió a cromatografía en columna instantánea (1:12 metanol/cloruro de metileno) para dar el compuesto del título (313 mg, 59% de rendimiento). ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.28-7.21 (m, 5H), 6.94-6.83 (m, 3H), 5.06-4.95 (m, 2H), 4.46-4.41 (m, 1H), 3.68 (s, 3H), 3.17-3.11 (m, 1H), 2.95-2.88 (m, 1H). CL/EM: tR = 2.11 min, 370 $(MH)^+$.

764
768

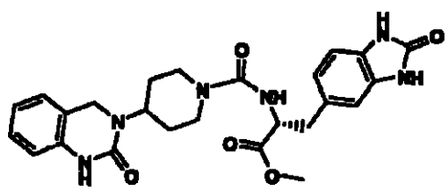
2-amino-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo



El (R)-1-(metoxicarbonil)-2-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)etilcarbamato de bencilo (265 mg, 0.72 mmol) y paladio en carbono al 10% (30 mg) en metanol (15 mL) se agitaron durante 1.5 h bajo 50 psi (3.51 kg/cm^2) de hidrógeno usando un aparato Parr. La mezcla de reacción se purgó con 3 ciclos de vacío/purga de nitrógeno. La mezcla de reacción luego se filtró a través de una almohadilla de Celite® y la almohadilla se enjuagó con varias porciones de metanol. El filtrado de metanol se evaporó para dar el compuesto del título (168 mg, rendimiento cuantitativo). ^{1}H-RMN (CD_3OD, 300 MHz) δ 6.97 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 3.71-3.64 (m, 1H), 3.67 (s, 3H), 3.04-2.89 (m, 2H). CL/EM: tR = 0.87 min, 236 $(MH)^+$.

Ejemplo 233

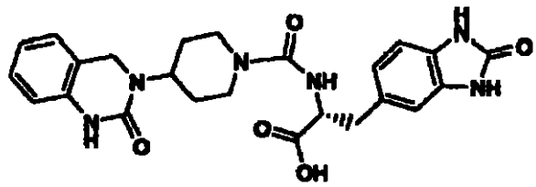
2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo



747
769

Preparado como se describe arriba por 2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.16-7.08 (m, 2H), 6.98-6.90 (m, 4H), 6.76 (d, J = 8.1 Hz, 1H), 4.52-4.47 (m, 1H), 4.39-4.35 (m, 1H9, 4.27 (s, 2H), 4.13-4.05 (m, 2H), 3.70 (s, 3H), 3.21-3.14 (m, 1H), 3.04-2.96 (m, 1H), 2.89-2.74 (m, 2H), 1.78-1.59 (m, 4H). CL/EM: tR = 1.77 min, 493 $(MH)^+$.

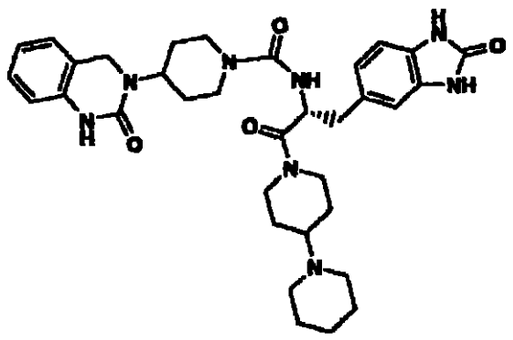
Ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-propanoico



Preparado como se describe arriba por ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.16-7.09 (m, 2H), 6.99-6.90 (m, 4H), 6.76 (d, J = 7.3 Hz, 1H), 4.53-4.48 (m, 1H), 4.28 (s, 2H), 4.13-4.03 (m, 2H), 3.07-2.97 (m, 1H), 2.89-2.77 (m, 2H), 1.79-1.60 (m, 4H), 1.28-1.21 (m, 1H). CL/EM: tR = 1.83 min, 479 $(MH)^+$.

Ejemplo 234

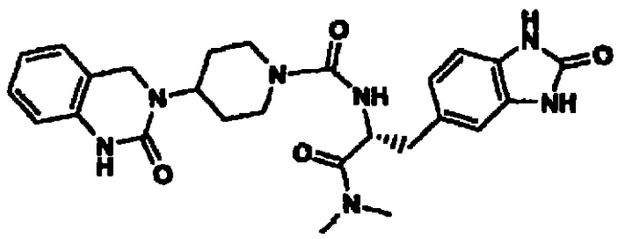
N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)-piperidin-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.17- 7.10 (m, 2H), 7.01 (s, 1H), 6.95-6.90 (m, 3H), 6.78 (d, J = 8.1 Hz, 1H), 4.98-4.93 (m, 1H), 4.62-4.55 (m, 1H), 4.41-4.33 (m, 2H), 4.20-4.16 (m, 2H), 4.04-3.96 (m, 1H), 3.05-2.85 (m, 7H), 2.71-2.57 (m, 1H), 2.53-2.32 (m, 1H), 1.86-1.76 (m, 2H), 1.70-1.61 (m, 8H), 1.50-1.41 (m, 2H), 1.03-0.89 (m, 1H), 0.10--0.02 (m, 1H). Espectro de masa: 629.22 $(MH)^+$.

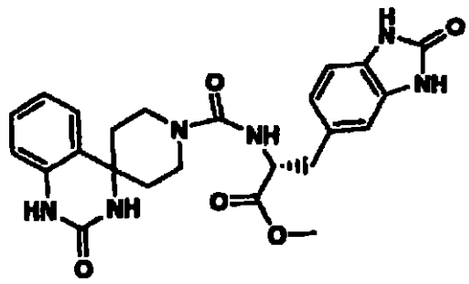
Ejemplo 235

N-((R)-1-(dimetilcarbamoil)-2-(2,3-dihidro-2-oxo-1H-banzo[d]imidazol-6-il)etil)-4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.96 min, 506 $(MH)^+$.

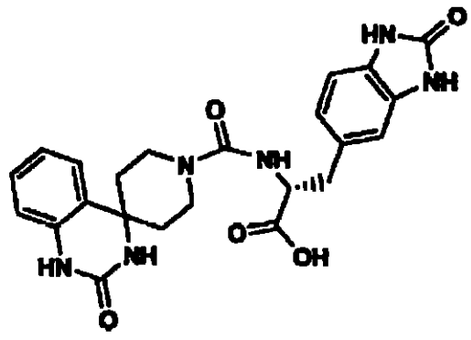
2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolina)carbonilamino]-3-2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo



Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato. ^{1}H-RMN (DMSO-d6, 500 MHz) δ 10.54 (s, 1H),

10.50 (s, 1H), 9.22 (s, 1H), 7.21 (s, 1H), 7.13-7.10 (m, 1H), 6.96-6.79 (m, 7H), 4.29-4.25 (m, 1H), 3.82-3.78 (m, 2H), 3.60 (s, 3H), 3.32-3.23 (m, 1H), 3.16-3.14 (m, 1H), 3.00-2.90 (m, 2H), 2.08 (s, 1H), 1.67-1.55 (m, 4H). CL/EM: t_R = 1.62 min, 479 $(MH)^+$.

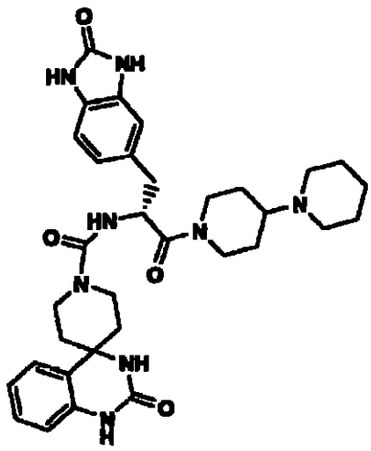
Ácido (R)-2-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-(1H)-quinazolina)carbonilamino]-3-2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoico



Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.19-7.14 (m, 1H), 7.05-6.95 (m, 5H), 6.81 (d, J = 7.7 Hz, 1H), 5.04-4.90 (m, 1H), 4.57-4.52 (m, 1H), 3.96-3.84 (m, 2H), 3.24-3.14 (m, 2H), 3.07-2.95 (m, 1H), 1.94-1.73 (m, 4H). CL/EM: t_R = 1.67 min, 465 $(MH)^+$.

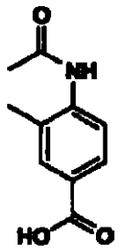
Ejemplo 236

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(2',3'-dihidro-2'-oxoespiro(piperidin-4,4'-(1H)-quinazolina)carboxamida



Preparado como se describió anteriormente por el ejemplo CL/EM: t_R = 1.55 min, 615 $(MH)^+$.

Ácido 4-Acetamido-3-metilbenzoico

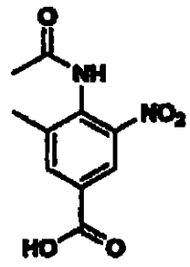


A una suspensión de ácido 4-amino-3-metilbenzoico (60 g, 0.40 mol) en cloruro de metileno (800 mL) se

900 774

agregó trietilamina (121 g, 1.19 mol). La solución se volvió clara. Luego, anhídrido acético (81 g, 0.79 mol) se agregó y la mezcla de reacción se agitó durante 60 h a temperatura ambiente. El solvente se evaporó. El residuo se diluyó con agua (400 mL) y se extrajo con acetato de etilo (3 x 600 mL). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtraron y se evaporaron para dar el compuesto del título como un sólido color marrón (43 g, 56% de rendimiento). ^{1}H-RMN (d_6-DMSO, 300 MHz) δ 9.36 (s, 1H), 7.77 (s, 1H), 7.10 (s, 2H), 2.27 (s, 3H), 2.10 (s, 3H). CL/EM: t_R = 1.194 $(MH)^+$.

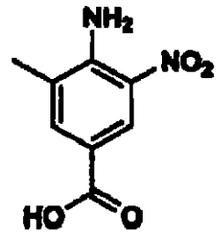
Ácido 4-Acetamido-3-metil-5-nitrobenzoico



A una solución de 60% ácido nítrico en ácido sulfúrico (410 mL) se agregó ácido 4-acetamido-3-metilbenzoico (43 g, 0.22 mol) en porciones pequeñas durante 40 minutos mientras se enfrió con un baño de hielo. Después de la adición de toda la amida se completó, la mezcla de reacción se agitó durante

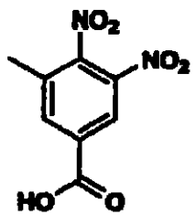
1 h a 0°C y luego se vació muy lentamente sobre 1500 mL de hielo. El sólido amarillo se colectó por filtración y se lavó con hielo frío con agua para dar el compuesto del título (38 g, 72% de rendimiento). ^{1}H-RMN (CD_3OD, 300 MHz) δ 8.29 (s, 1H), 8.18 (s, 1H), 2.39 (s, 3H), 2.16 (s, 3H). Espectro de masa: 237 $(MH)^+$.

Ácido 4-amino-3-metil-5-nitrobenzoico



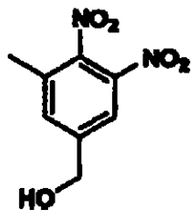
Una suspensión de ácido 4-acetamido-3-metil-5-nitrobenzoico (38 g, 0.16 mol) en 3N ácido clorhídrico (800 mL) se calentó a reflujo durante 8 h y luego se agitó a temperatura ambiente durante 8 h. El sólido amarillo se colectó por filtración y se transfirió a un matraz de 2 L con una mezcla de cloruro de metileno y metanol. El solvente se evaporó bajo alto vació para dar el compuesto del título (23 g, 74% de rendimiento). ^{1}H-RMN (DMSO-d6, 300 MHz) δ 12.79 (bs, 1H), 8.46 (s, 1H), 7.79 (s, 1H), 7.61 (s, 2H), 2.34 (s, 3H). ^{13}C-RMN 75 MHz) δ 166.0, 147.0, 135.1, 130.0, 126.4, 125.9, 116.7, 17.9. CL/EM: t_R = 1.23 min, 195 $(MH)^-$.

Ácido 5-dinitrobenzoico



A una suspensión de ácido 4-amino-3-metil-5-nitrobenzoico (5.0 g, 25.5 mmol) en ácido trifluoroacético (200 mL) se agregó peróxido de hidrógeno (50 % en peso, 15 mL). La mezcla de reacción se calentó a 50°C durante 2 h y la solución eventualmente se siguió a partir de una solución clara anaranjada oscura a una solución clara amarilla pálida. La mezcla de reacción se vació lentamente en agua con hielo (800 mL). El sólido se colectó por filtración y se secó bajo vacío para dar el compuesto del título como un sólido blanco opaco (4.0 g, 70% de rendimiento). ^{1}H-RMN (CD_3OD, 300 MHz) δ 8.59 (s, 1H), 8.40 (s, 1H), 2.45 (s, 3H). ^{13}C-RMN (CD_3OD, 75 MHz) δ 165.8, 147.4, 142.0, 139.3, 134.8, 134.6, 125.4, 17.2. Espectro de masa: 225.14 $(MH)^-$.

(3-Metil-4,5-dinitrofenil)metanol

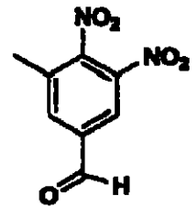


Una solución de ácido 3-metil-4,5-dinitrobenzoico (4.0

g, 17.7 mmol) en tetrahidrofurano (200 mL) se enfrió a -70°C con un baño de hielo seco/acetona. A esta solución se agregó tetrahidrofurano de borano (1M en tetrahidrofurano, 35.4 mL). La mezcla de reacción se permitió calentar lentamente a temperatura ambiente y se agitó durante 16 h. La reacción se incompleto, se volvió a enfriar a -50°C y tetrahidrofurano de borano adicional en tetrahidrofurano (1M en tetrahidrofurano, 35.4 mL) se agregó. Otra vez, la mezcla de reacción se permitió calentar lentamente a temperatura ambiente durante la noche. La reacción se apagó con una mezcla de ácido acético y agua (1:1, 30 mL) mientras se enfrió a 0°C. Después de agitarse durante 30 min, todo el solvente orgánico se evaporó y el material acuoso se neutralizo por vaciar en hielo frío bicarbonato de sodio saturado (350 mL) en pequeñas porciones. La capa acuosa se extrajo con acetato de etilo. Los extractos se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se evaporaron. El residuo se sometió a cromatografía en columna instantánea (1:2 hexanos/acetato de etilo) para dar el compuesto del título (3.2 g, 86% de rendimiento). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.00 (s, 1H), 7.62 (s, 1H), 4.82 (s, 2H), 2.41 (s, 3H). ^{13}C-RMN ($CDCl_3$, 75 MHz) δ 144.5, 143.3, 140.9, 134.3, 132.9, 120.8, 63.0, 17.4.

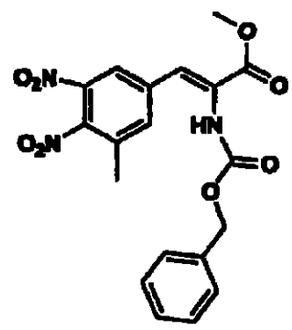
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3-Metil-4,5-dinitrobenzaldehido



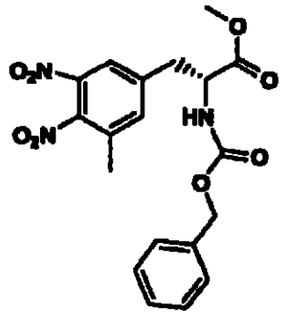
En un matraz secado a la flama, óxido de manganeso (IV) (36.0 g, 414 mmol) se secó azeotrópicamente con tolueno. Luego, una solución de (3-metil-4,5-dinitrofenil)metanol (3.2 g, 15 mmol) en cloroformo (100 mL) se transfirió a el matraz que contiene el dióxido de manganeso. La mezcla de reacción se calentó a 50°C con agitación durante 3 h. Durante la terminación de la reacción, la mezcla de reacción se filtró a través de una almohadilla de celite® para remover dióxido de manganeso y el Celite se lavó con cloroformo varias veces. El filtrado se evaporó para dar el compuesto del título (1.4 g, 44% de rendimiento). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 10.09 (s, 1H), 8.51 (s, 1H), 8.16 (s, 1H), 2.51 (s, 3H).

(Z)-1-(metoxicarbonil)-2-(3-metil-4,5-dinitrofenil)vinilcarbamato de bencilo



A una solución de éster de trimetilo de N-(benciloxicarbonil)-α-fofonoglicina (2.4 g, 7.3 mmol) en tetrahidrofurano (40 mL) a -78°C se agregó 1,1,3,3-tetrametilguanidina (729 mg, 6.33 mmol) y la mezcla se agitó durante 1 h a -78°C. A esta mezcla se agregó una solución de 3-metil-4,5-dinitrobenzaldehido (1.4 g, 6.7 mmol) en tetrahidrofurano (15 mL). La mezcla de reacción se permitió calentar lentamente a temperatura ambiente y luego se agitó durante 16 h a temperatura ambiente. El solvente se evaporó y el residuo se sometió a cromatografía en columna instantánea (gradiente, 1:2 hasta 1:1 acetato de etilo/hexano). El producto luego se recristalizó a partir de acetato de etilo/hexanos: para dar el compuesto del título (1.7 g, 62% de rendimiento). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.55 (s, 1H), 7.33-7.22 (m, 6H), 6.94 (bs, 1H), 5.06 (s, 2H), 3.89 (s, 3H), 2.29 (s, 3H). ^{13}C-RMN ($CDCl_3$, 75 MHz) δ 164.7, 152.5, 143.1, 140.6, 137.7, 137.0, 135.3, 132.5, 128.8, 128.7, 128.6, 127.1, 123.5, 68.3, 53.5, 17.4. Espectro de masa: 414.20 $(MH)^-$.

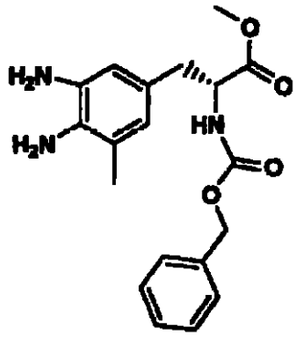
(R)-1-(metoxicarbonil)-2-(3-metil-4,5-dinitrofenil)etilcarbamato de bencilo



En una bolsa de guante que se sometió a 3 ciclos de purga de vacío/nitrógeno, en un matraz de reacción AIRFREE (Schlenk) se equipó con una barra de agitación se cargó con trifluorometilsulfonato de (-)-1,2-bis((2R,5R-2,5-dietilfosfolano)benceno(ciclooctadieno)rodio (I) (125 g, 0.173 mmol, 4 mol%), se selló con un septo de goma, y se removió de la bolsa de guante. El (Z)-1-(metoxicarbonil)-2-(3-metil-4,5-dinitrofenil)vinilcarbamato (1.65 g, 3.97 mmol) se pesó en un segundo matraz de reacción AIRFREE® (Schlenk) equipado con una barra de agitación y se selló con un septo de goma. Después de 3 ciclos de purga vacío/nitrógeno, esto se disolvió en una mezcla de cloruro de metileno anhidro (40 mL). El solvente se desoxigeno previo a la adición por rocío con nitrógeno durante al menos 1 h. Una vez en la solución, la mezcla se volvió a someter a 3 ciclo de purga vacío/nitrógeno. La solución de ácido deshidroamino se introduce en el matraz de reacción (Schlenk) que contienen el catalizador por medio de cánula. La mezcla de reacción se sometió a 5 ciclo de purga vacío/hidrógeno antes de abrir el matraz a 1 atmósfera de hidrógeno. Después de 16 h, la mezcla de reacción se purgó con 3 ciclos de purga vacío/nitrógeno. El solvente se evaporó y el residuo se sometió a cromatografía de columna (1:1 acetato de etilo/hexanos) para dar el compuesto del título (1.58 g, 95%). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.75 (s, 1H), 7.39-7.33 (m, 6H), 5.37 (d, J = 7.0 Hz,

1H), 5.15-5.04 (m, 2H), 4.70-4.46 (m, 1H), 3.77 (s, 3H), 3.30 (dd, J = 13.9, 5.5 Hz, 1H), 3.12 (dd, J = 13.9, 6.2 Hz, 1H), 2.33 (s, 3H). CL/EM: t_R = 2.71 min, 418 $(MH)^+$.

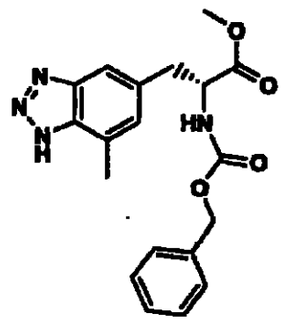
(R)-1-(metoxicarbonil)-2-(3,4-diamino-5-metilfenil)etilcarbamato de bencilo



El formiato de amonio sólido (755 mg, 11.9 mmol) se agregó en pequeñas porciones a 0°C a una suspensión de (R)-1-(metoxicarbonil)-2-(3-metil-4,5-dinitrofenil)etilcarbamato de bencilo (500 mg, 1.20 mmol) y polvo de zinc (470 mg, 7.19 mmol) en metanol (20 mL, se desgasifico con nitrógeno durante 2 h). La mezcla resultante se agitó a temperatura ambiente durante 60 h. La reacción no se completó. La mezcla de reacción se volvió a enfriar a 0°C y polvo de zinc adicional (470 mg, 7.19 mmol) se agregó. La reacción se agitó durante 4 h tiempo al cual la reacción se completó. La mezcla de reacción se filtró para remover zinc. El filtrado se evaporó. Una mezcla de tolueno y acetato de etilo (1:1) se agregaron, seguido por ácido acético (2 mL). La mezcla se diluyó adicional hasta que todos los sólidos orgánicos se disolvieron,

luego esto se lavó con agua, salmuera, se secó sobre sulfato de sodio, y se evaporó. El residuo luego se re-disolvió en acetato de etilo y cloruro de hidrógeno 4N en dioxano (4 mL) se agregó. El solvente se evaporó para dar el compuesto del título como la sal de clorohidrato (515 mg, rendimiento cuantitativo). ^{1}H-RMN (CD_3OD, 300 MHz) δ 7.35-7.30 6.94-6.93 (m, 2H), 5.03 (s, 2H), 4.42-4.37 (m, 1H), 3.70 (s, 3H), 3.09-3.03 (m, 1H), 2.87-2.79 (m, 1H), 2.25 (s, 3H). CL/EM: t_R = 1.79 min, 358 $(MH)^+$.

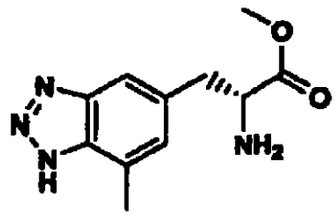
(R)-1-(metoxicarbonil)-2-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)etilcarbamato



A una solución de (R)-1-(metoxicarbonil)-2-(3,4-diamino-5-metilfenil)etilcarbamato de bencilo (250 mg, 0.58 mmol) en ácido acético (6 mL) y agua (10 mL) se agregó a una solución de nitrito de sodio (40 mg, 0.58 mmol) en agua (1 mL), gota a gota durante varios minutos a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente durante 30 minutos, luego se enfrió a 0°C. Una mezcla de hidróxido de amonio y agua (1:1, 15 mL) se agregó hasta ajustar el pH a 11. La mezcla se extrajo con acetato de etilo dos veces. Las capas orgánicas se lavaron con salmuera y se secaron sobre

sulfato de sodio. Después de la filtración, los solventes se removieron in vacuo y el residuo se purificó por cromatografía de columna instantánea (1:1 acetato de etilo/hexanos) en gel de sílice para proporcionar el compuesto del título como un sólido color marrón (155 mg, 72% de rendimiento). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.34 (s, 1H), 7.32-7.28 (m, 6H), 6.93 (s, 1H), 5.40 (d, J = 8.1 Hz, 1H), 5.13-5.02 (m, 2H), 4.76-4.69 (m, 1H), 3.73 (s, 3H), 3.28 (dd, J = 13.9, 5.5 Hz, 1H), 3.16 (dd, J = 13.9, 6.2 Hz, 1H), 2.64 (s, 3H). CL/EM: t_R = 2.30 min, 369 $(MH)^+$.

2-amino-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)propanoato de (R)-metilo

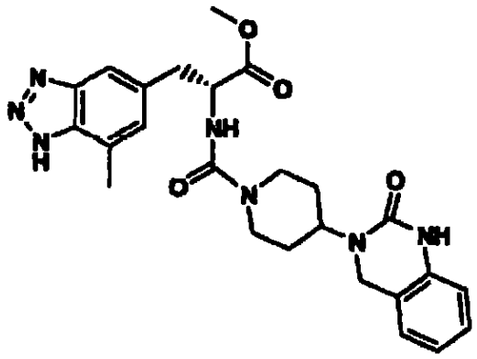


El (R)-1-(metoxicarbonil)-2-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)etilcarbamato de bencilo (146 mg, 0.40 mmol) se disolvió en 12 mL de una solución de 4.4% ácido fórmico en metanol. El matraz de reacción que contiene esta solución se equipó con una barra de agitación magnética y luego se mojó con nitrógeno durante varios minutos. A la solución se agregó paladio en carbono (10%, 200 mg) y la reacción se agitó durante 16 h a temperatura ambiente bajo atmósfera de nitrógeno. La mezcla de reacción se filtró a través de una almohadilla de Celite® varias veces con metanol. El filtrado se evaporó para dar el compuesto del

XP 284

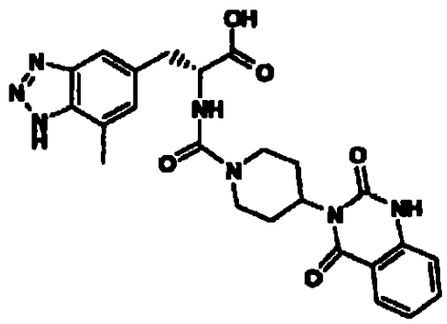
título (rendimiento cuantitativo). ^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.40 (bs, 1H), 7.55 (s, 1H), 7.14 (s, 1H), 4.29-4.24 (m, 1H), 3.78 (s, 3H), 3.39-3.19 (m, 2H), 2.69 (s, 3H). CL/EM: t_R = 1.18 min, 235 $(MH)^+$.

2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)propanoato de (R)-metilo



Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato. CL/EM: t_R = 2.17 min, 492 $(MH)^+$.

Ácido (R)-2-(4-(1,2-dihidro-2,4-dioxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)propanoico

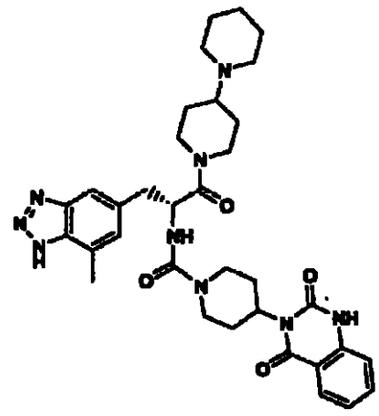


XH 735

Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. CL/EM: t_R = 2.11 min, 492 $(MH)^+$.

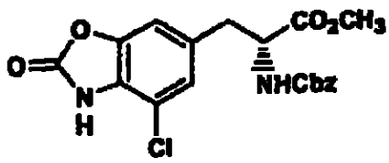
Ejemplo 237

4-(1,2-dihidro-2,4-dioxoquinazolina-3-(4H)-il)-N-((R)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. ^{1}H-RMN (CD_3OD, 300 MHz) δ 8.01 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.28-7. 11 (m, 4H), 5.06-5.00 (m, 1H), 4.70-4.60 (m, 1H), 4.31-4.17 (m, 2H), 3.50-3.44 (m, 1H), 3.20-2.82 (m, 7H), 2.75-2.47 (m, 6H), 2.12-2.02 (m, 2H), 1.93-1.67 (m, 11H), 1.37-1.28 (m, 2H), 0.97-0.79 (m, 2H), 0.23-0.09 (m, 1H). Espectro de masa: 642 $(MH)^+$.

Éster metilo del ácido (R)-2-Benciloxicarbonilamino-3-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propanoico

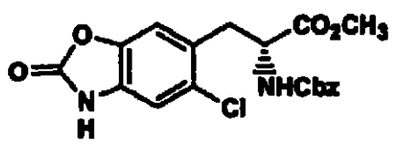


Una mezcla de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propanoico (373 mg, 1.01 mmol), N-clorosuccinimida (168 mg, 1.26 mmol), gel de sílice (EM Scientific, 230-400 malla, 3.73 g) en dicloroetano (20 mL) se calentó a 90°C durante 16 h. Después de enfriarse a temperatura ambiente, los solventes se removieron in vacuo. El residuo se sometió a cromatografía de gel de sílice usando acetato de etilo/hexanos (1:2) como eluyente para proporcionar el compuesto del título (40 mg, 9.8%), también éster de metilo del ácido 2-benciloxicarbonilamino-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (78 mg, 19%). La estructura se confirmó por RMN 2D y al comparar con la éster metilo del ácido 2-benciloxicarbonilamino-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propanoico preparado por la reacción mostrada a continuación. ^{1}H-RMN (CD_3COCD_3, 500 MHz) δ 7.37-7.27 (m, 5H), 7.18 (d, J = 1.0 Hz, 1H), 7.16 (s, 1H), 6.76 (d, J = 8.5 hz, 1H), 5.06 (d, J = 5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.55-4.51 (m, 1H), 3.72 (s, 3H), 3.26 (dd, J = 14.0, 5.0

847787

Hz, 1H), 3.04 (dd, J = 14.0, 9.5 Hz, 1H); ^{13}C-RMN (CD_3COCD_3,125 MHz) δ 172.2, 156.4, 154.0, 144.8, 137.6, 133.3, 128.7, 128.2, 128.0, 127.9, 125.0, 66.3, 55.9, 52.0, 37.3; Espectro de masa 405 (MH^+).

Éster metilo del ácido (R)-2-benciloxocarbonilamnio-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propanoico

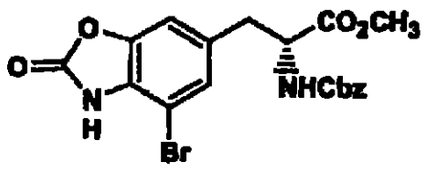


La N-clorosuccinimida (315 mg, 2.36 mmol) se agregó a una solución de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (700 mg, 1.89 mmol) en ácido acético (50 mL) a temperatura ambiente. La mezcla se calentó a 100°C durante 16h. Después de esto se enfrió a temperatura ambiente, los solventes se removieron in vacuo. El residuo se sometió a cromatografía de gel de sílice usando acetato de etilo/hexanos (4:6) luego (1:1) como eluyente para proporcionar el compuesto del título como un sólido amarillo opaco (242 mg, 32%). La estructura del producto se confirmo por RMN 2D. ^{1}H-RMN (CD_3COCD_3, 500 MHz) δ 10.47 (s, 1H), 7.36-7.28 (m, 6H), 7.20 (s, 1H), 6.80 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.65-4.60

644 288

(m, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.0, 5.0 Hz, 1H), 3.08 (dd, J = 14.0, 10.5 Hz, 1H); ^{13}C-RMN (CD_3COCD_3, 125 MHz) δ 172.2, 156.5, 154.5, 143.1, 137.5, 130.8, 129.0, 128.9, 128.7, 128.2, 128.0, 112.8, 110.9, 66.3, 54.3, 52.1, 35.8 ; Espectro de masa 405 (MH^+).

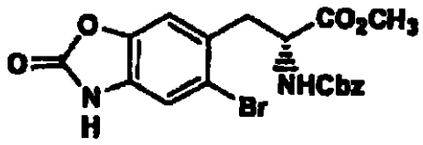
Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



Una mezcla de éster de metilo del ácido 3-dihidro-benzooxazol-6-il)-propiónico (418 mg, 1.13 mmol), N-bromosuccinimida (221 mg, 1.24 mmol), gel de sílice (EM Scientific, 230-400 malla, 2.51 g) y cloruro de metileno (70 mL) se agitó a temperatura ambiente durante 16 h. Los solventes se removieron in vacuo y el residuo se sometió a cromatografía de gel de sílice usando acetato de etilo/hexanos (2:3) como eluyente para proporcionar el compuesto del título. ^{1}H-RMN (CD_3COCD_3, 500 MHz) δ 10.71 (s, 7.35-7.28 (m, 6H), 7.21 (s, 1H), 6.75 (d, J = 7.5 Hz, 1H), 5.06 (d, 12.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.56-4.51 (m, 1H), 3.73 (s, 3H), 3.26 (dd, J = 14.0, 5.0 Hz, 1H), 3.03 (dd, J = 14.0, 10.0 Hz, 1H); ^{13}C-RMN (CD_3COCD_3, 125 MHz) δ

172.2, 156.4, 153.8, 144.4, 137.6, 133.7, 129.8, 128.7, 128.2, 128.0, 127.8, 110.1, 100.9, 66.3, 55.9, 52.0, 37.3; Espectro de masa 448.03 (MH^+).

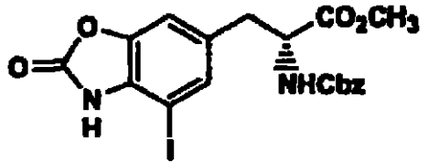
Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



Una mezcla de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (1.07 g, 2.89 mmol), N-bromosuccinimida (643 mg, 3.61 mmol), y ácido acético (150 mL) se calentó a 105°C durante 14 h. Después de enfriarse a temperatura ambiente, los solventes se removieron in vacuo. El residuo se sometió a cromatografía de gel de sílice usando acetato de etilo/hexanos (2:3), luego (1:1) como eluyente para proporcionar el compuesto del título (446 mg, 34%). La estructura del compuesto del título se confirmó por RMN 2D. ^{1}H-RMN (CD_3COCD_3, 500 MHz) δ 10.46 (s, 1H), 7.36-7.28 (m, 7H), 6.82 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.67-4.62 (m, 1H), 3.73 (s, 3H), 3.43 (dd, J = 14.0, 5.0 Hz, 1H), 3.10 (dd, J = 14.0, 10.5 Hz, 1H); ^{13}C-RMN (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 154.2, 143.7, 137.6,

131.1, 130.6, 128.7, 128.0, 118.2, 113.9, 112.9, 66.2, 54.3, 52.1, 38.3; Espectro de masa 448.03 (MH^+).

Éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico

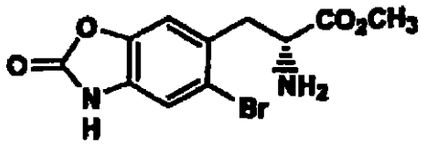


Una mezcla de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico (324 mg, 0.87 mmol), $I(PyH)_2BF_4$ (409 mg, 1.08 mmol), gel de sílice (EM Scientific, 230-400 malla, 3.24 g) y dicloroetano (20 mL) se calentó a 90°C durante 6 h. Después de enfriarse a temperatura ambiente los solventes se removieron in vacuo. El residuo se sometió a cromatografía de gel de sílice usando acetato de etilo/hexanos (1:2) como eluyente para proporcionar el compuesto del título (175 mg, 40%). La estructura del compuesto del título se confirmó por RMN 2D. ^{1}H-RMN (CD_3COCD_3, 500 MHz) δ 10.47 (s, 1H), 7.46 (s, 1H), 7.37-7.29 (m, 5H), 7.22 (s, 1H), 6.74 (d, J = 8.5 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.54-4.49 (m, 1H), 3.72 (s, 3H), 3.23 (dd, J = 14.0, 5.0 Hz, 1H), 3.01 (dd, J = 14.0, 9.5 Hz, 1H); ^{13}C-RMN (CD_3COCD_3, 125 MHz) δ 172.2, 156.4, 153.4, 143.3, 137.6, 134.1, 133.64,

817 791

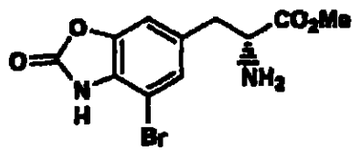
133.60, 128.7, 128.2, 128.0, 110.7, 71.1, 66.3, 56.0, 52.0, 37.1; Espectro de masa 496.01 (MH^+).

Éster metilo del ácido (R)-2-amino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



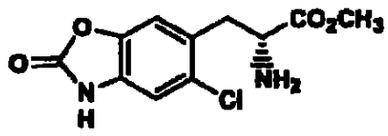
El trimetilsililyoduro (73 mL, 0.73 mmol) se agregó a una solución de éster de metilo del ácido (R)-2-benciloxicarbonilamino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico secado azeotrópicamente (146 mg, 0.33 mmol) en acetonitrilo (10 mL) a temperatura ambiente, y la mezcla resultante se agitó a temperatura ambiente durante 2 h. La trietilamina (0.12 mL) se agregó y la mezcla se agitó a temperatura ambiente durante 15 min. Los solventes se removieron in vacuo, y el residuo se extrajo con acetato de etilo. Los orgánicos combinados se lavaron con bicarbonato de sodio y salmuera, se secaron sobre sulfato de sodio y se filtraron. Los solventes se removieron y el residuo se usó directamente en la siguiente etapa. Espectro de masa 315.10 $(MH)^+$.

Éster de metilo del ácido (R)-2-Amino-3-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



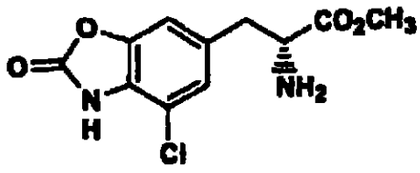
Preparado como se describió anteriormente por el éster de metilo del ácido 3-dihidro-benzooxazol-6-il)-propiónico. Espectro de masa 315.06 $(MH)^+$.

Éster de metilo del ácido (R)-2-amino-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



Preparado como se describió anteriormente por el éster de metilo del ácido (R)-2-amino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. Espectro de masa 271.10 $(MH)^+$.

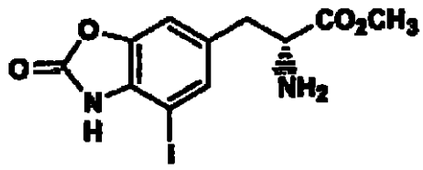
Éster metilo del ácido (R)-2-Amino-3-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico



Preparado como se describió anteriormente por el éster

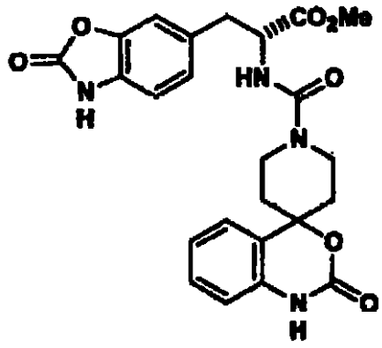
de metilo del ácido (R)-2-amino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. Espectro de masa 271.16 $(MH)^+$.

Éster de metilo del ácido (R)-2-Amino-3-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico:



Preparado como se describió anteriormente por el éster de metilo del ácido (R)-2-amino-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-propiónico. Espectro de masa 363.04 $(MH)^+$.

Éster de metilo del ácido (R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-2-{[2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazin)-1-carbonil]-amino}-propiónico

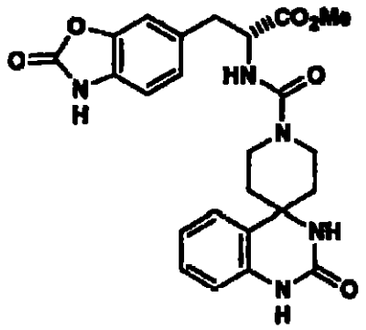


Preparado como se describió anteriormente por 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de

794

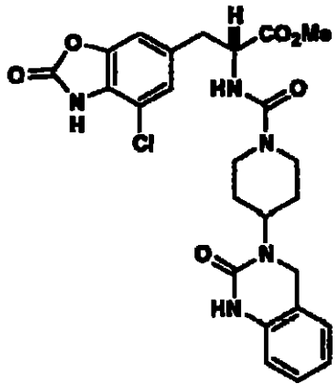
(R)-metilo. Espectro de masa 481.20 $(MH)^+$.

Éster de metilo del ácido (R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-2-{[2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. Espectro de masa 480.24 $(MH)^+$.

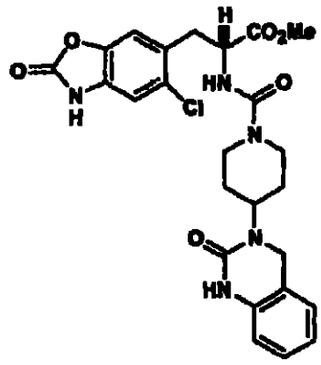
Éster de metilo del ácido (R)-3-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



824 795

Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. Espectro de masa 528.16 $(MH)^+$.

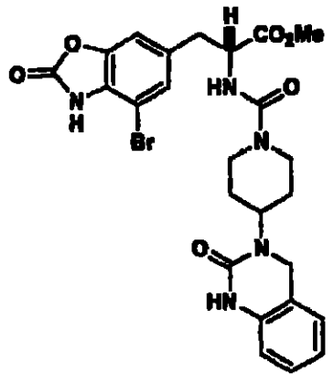
Éster de metilo del ácido (R)-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. Espectro de masa 528.20 $(MH)^+$.

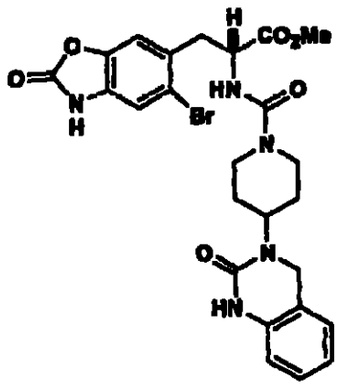
796

Éster de metilo del ácido (R)-3-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato. Espectro de masa 572.20 $(MH)^+$.

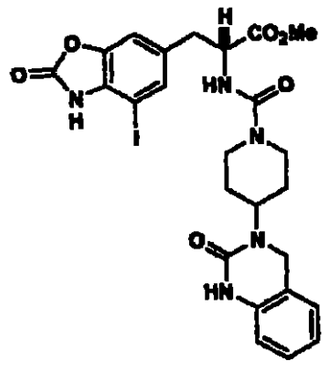
Éster de metilo del ácido (R)-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



797

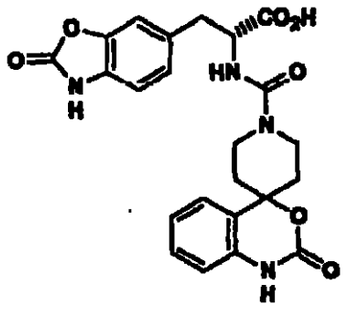
Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. Espectro de masa 572.15 $(MH)^+$.

Éster de metilo del ácido (R)-3-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el 2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoato de (R)-metilo. Espectro de masa 620.20 $(MH)^+$.

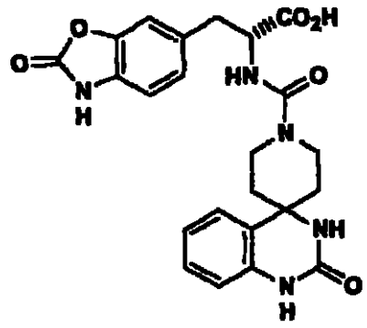
Ácido (R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-2-{[2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carbonil]-amino}-propiónico



824
798

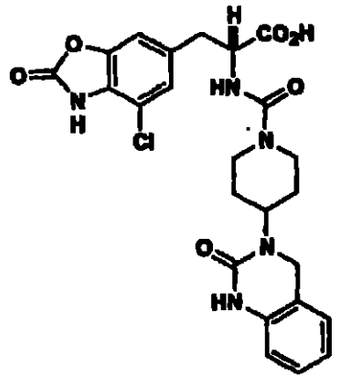
Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 467.18 $(MH)^+$.

Ácido (R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-2-{[2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 466.20 $(MH)^+$.

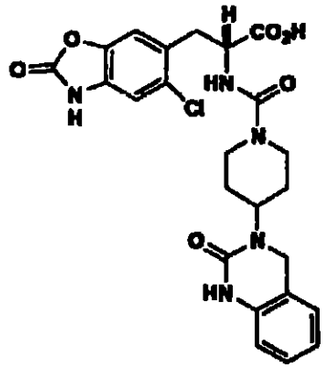
Ácido (R)-3-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



825 799

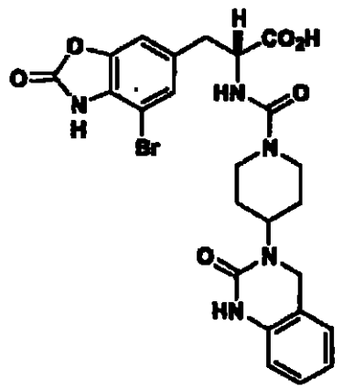
Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 514.20 $(MH)^+$.

Ácido (R)-3-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino)-propiónico



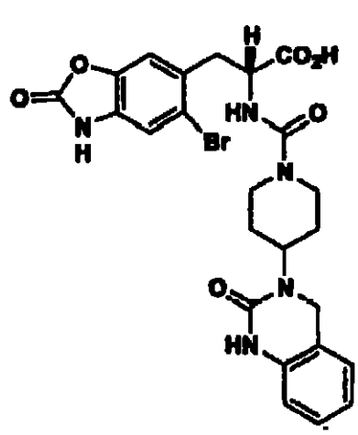
Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 514.24 $(MH)^+$.

Ácido (R)-3-(4-Bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



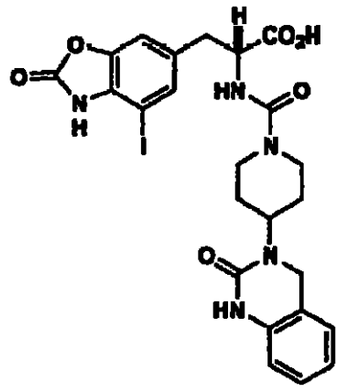
Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)il)propanoico. Espectro de masa 558.30 $(MH)^+$.

Ácido (R)-3-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 558.25 $(MH)^+$.

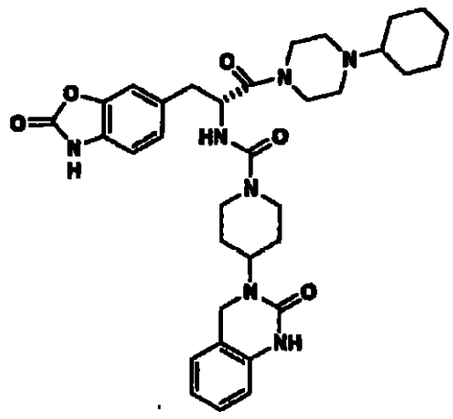
Ácido (R)-3-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el ácido (R)-2-(4-(1,2-dihidro-2-oxoquinazolina-3-(4H)-il)piperidin-1-carboxamido)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)propanoico. Espectro de masa 606.10 $(MH)^+$.

Ejemplo 238

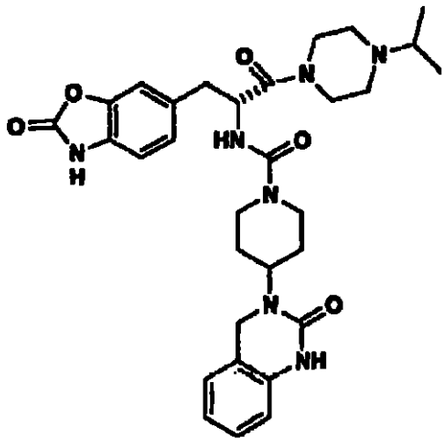
[2-(4-ciclohexil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.80 min, 630.37 $(MH)^+$.

Ejemplo 239

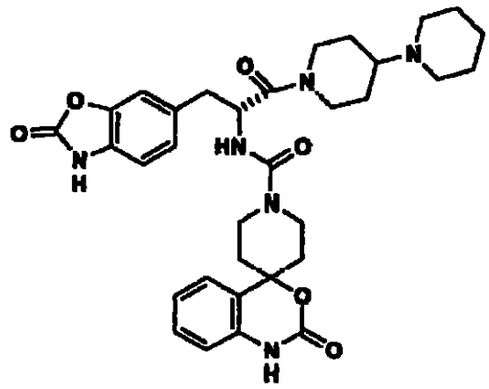
[2-(4-isopropil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.71 min, 590.34 $(MH)^+$.

Ejemplo 240

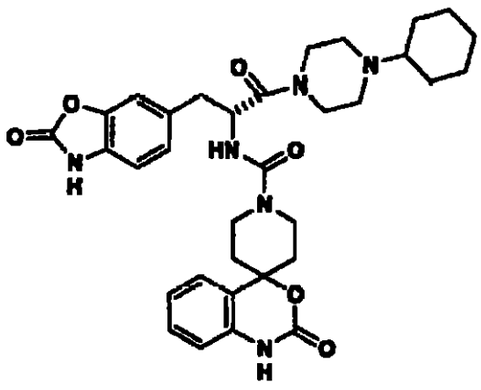
(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida



Preparado como se describió anteriormente por el ejemplo CL/EM: t_R = 1.64 min, 617.34 $(MH)^+$.

Ejemplo 241

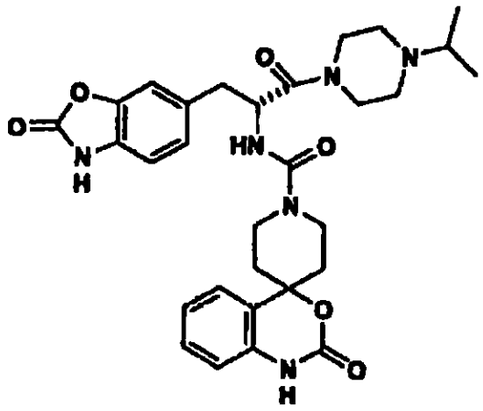
(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.69 min, 617.35 $(MH)^+$.

Ejemplo 242

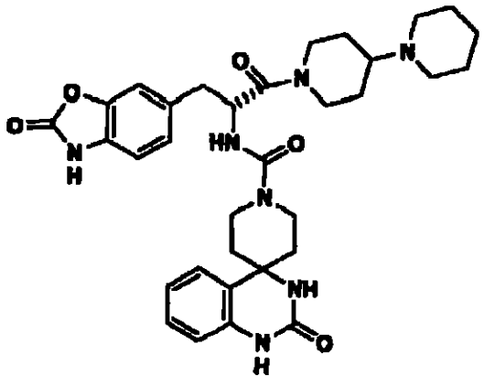
(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.57 min, 577.32 $(MH)^+$.

Ejemplo 243

(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida

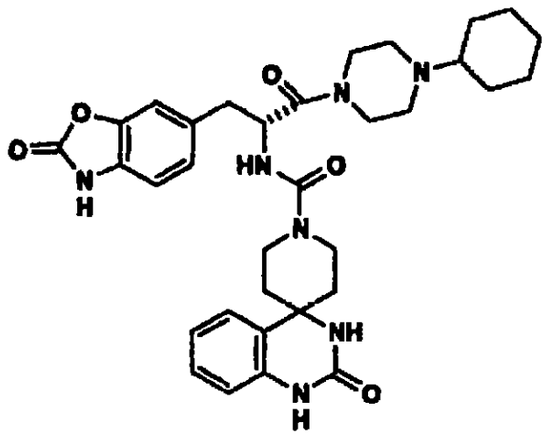


231+805

Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.74 min, 616.37 $(MH)^+$.

Ejemplo 244

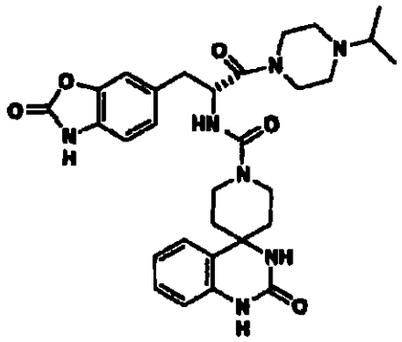
(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida



Preparado como anteriormente: CL/EM: t_R = 1.79 min, 616.36 $(MH)^+$.

Ejemplo 245

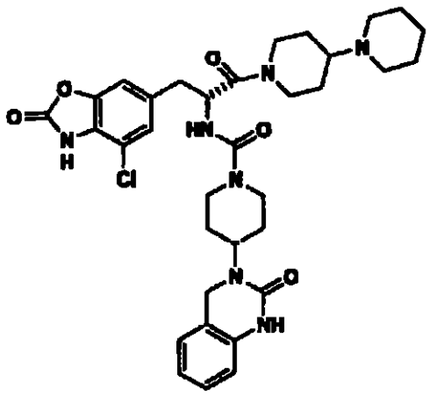
(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.67 min, 576.34 $(MH)^+$.

Ejemplo 246

[2-[1,4']bipiperidinil-1'-il-1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico

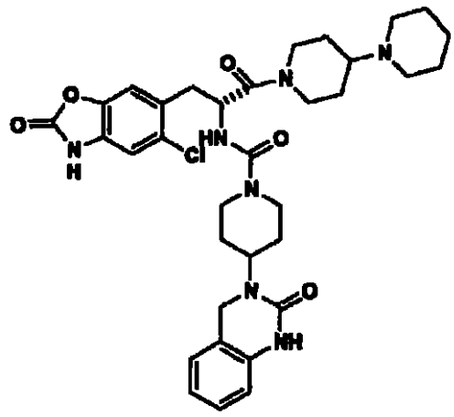


Preparado como se describió anteriormente por el ejemplo

231. CL/EM: t_R = 91 min, 664.35 $(MH)^+$.

Ejemplo 247

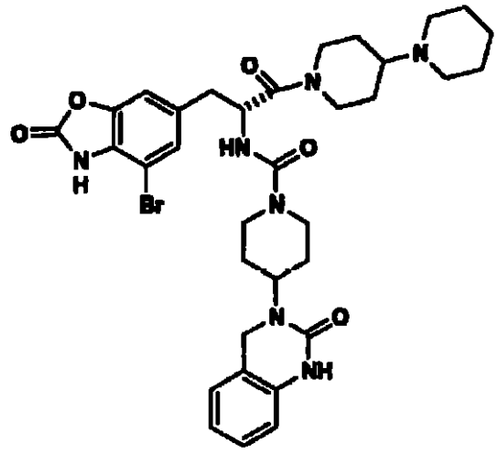
[2-[1,4']bipiperidinil-1'-il-1-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.91 min, 664.34 $(MH)^+$.

Ejemplo 248

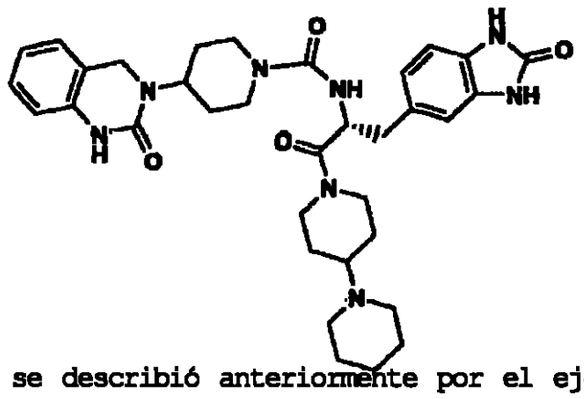
[2-[1,4']bipiperidinil-1'-il-1-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.96 min, 708.31 $(MH)^+$.

Ejemplo 249

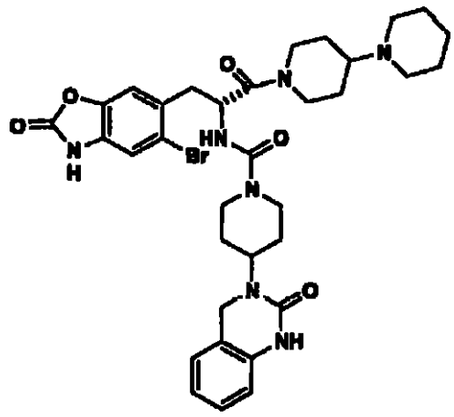
[2-[1,4']bipiperidinil-1'-il-1-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo CL/EM: t_R = 1.96 min, 708.31 $(MH)^+$.

Ejemplo 250

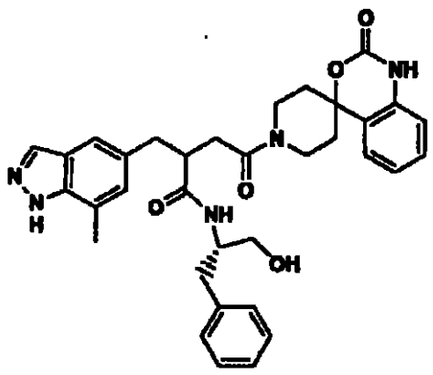
[2-[1,4']bipiperidinil-1'-il-1-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 231. CL/EM: t_R = 1.97 min, 756.36 $(MH)^+$.

Ejemplo 251

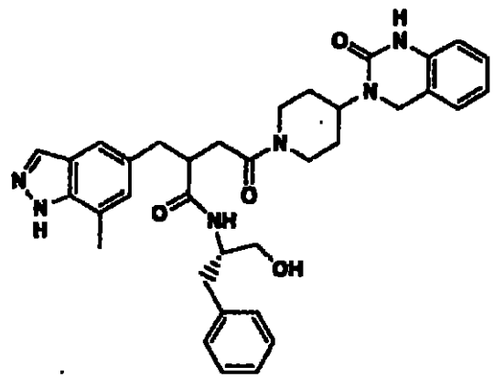
(±)-N-(1-bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butiramida



Preparado como se describió anteriormente por el (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = 38 min, 596 $(MH)^+$.

Ejemplo 252

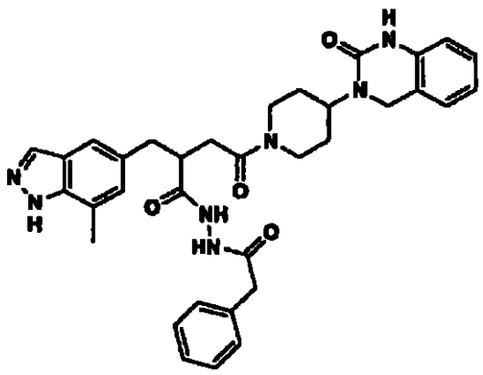
(±)-N-(1-bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butiramida



Preparado como se describió anteriormente por el (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R =1.50 min, 609 $(MH)^+$. ^1H RMN (400 MHz, CD_3OD) 7.90 (1H, s), 7.64-7.84 (1H, m), 6.71-7.42 m), 4.58 (1H, m), 3.82-4.50 (6H, m), 2.21-3.52 (13H, m), 1.42-1.87 (4H, m).

Ejemplo 253

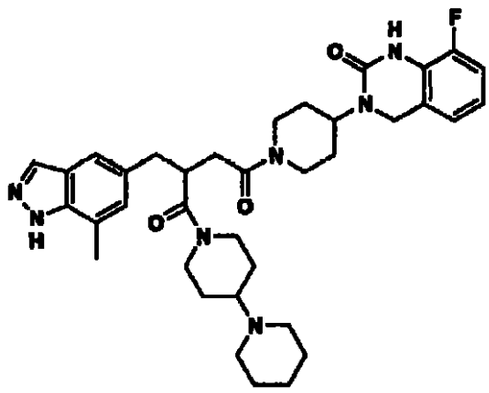
N'-{2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butiril}-hidrazida del ácido (±)-fenil-acético



Preparado como se describió anteriormente por la (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxanina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = 43 min, 630 $(M+Na)^+$.

Ejemplo 254

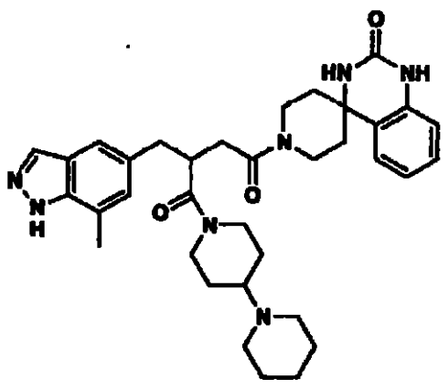
(±)-1-[1,4']Bipiperidinil-1'-il-4-[4-(8-fluoro-2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-2-(7-metil-1H-indazol-5-ilmetil)-butano-1,4-diona



Preparado como se describió anteriormente por (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = min, 644 $(MH)^+$. ^1H RMN (400 MHz, $CDCl_3$) δ 8.00 (1H, s), 6.82-7.40 (6H, m), 4.48-4.70 (3H, m), 4.31 (2H, s), 3.85-4.11 (2H, m), 3.65 (1H, m), 2.70-3.16 (5H, m), 2.53 (3H, s), 0.72-2.52 (23H, m).

Ejemplo 255

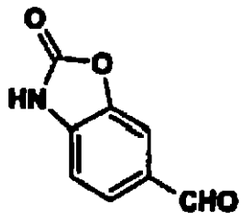
(±)-1-[1,4']biperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina]-butano-1,4-diona



Preparado como se describió anteriormente por (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: 612 $(MH)^+$.

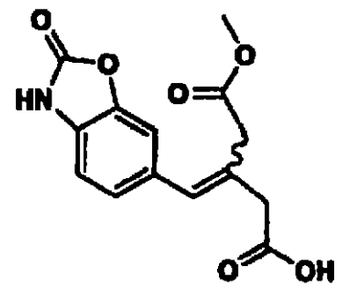
813

2-oxo-2,3-dihidro-benzooxazol-6-carbaldehído



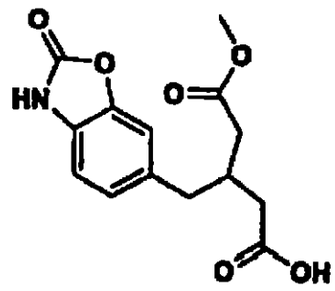
Una solución de 6-bromo-3H-benzooxazol-2-ona(0.9236g, 4.31 micromoles) en tetrahidrofurano anhidro (25 mL) y (3 mL) bajo nitrógeno se enfrió a -78°C antes de la adición de n-butillitio (2.5M en hexano) (3.8 mL, 2.2 equiv). Después de agitarse durante 10 minutos a -78°C, 24 mL de sec-butillitio (1.4 M en ciclohexano, 8 equiv) se agregó. La reacción se agitó mientras se calentó lentamente a -40°C. Cuando esta temperatura se logró, la reacción se apagó por la adición de metanol. La mezcla de reacción se concentró in vacuo y agua se agregó. La capa acuosa se acidificó con HCl 1N (ca. pH 5) y se extrajo con acetato de etilo (3 x 50 mL), se secó sobre sulfato de sodio, se filtró y se concentró para dar el producto, 0.6402 g (91%). EM (ESI) 164 $(MH)^+$. ^1H RMN (400 MHz, DMSO-d6) δ 9.90 (1H, s), 7.79 (1H, d, J = 8.0 Hz), 7.74 (1H, s), 7.28 (1H, d, J = 8.0 Hz).

Éster de monometilo del ácido 3-(2-Oxo-2,3-dihidro-benzooxazol-6-ilmetilen)-pentandioico



Preparado como se describió anteriormente por el éster de 1-metilo del ácido 2-(7-metil-1H-indazol-5-ilmetileno)-succínico (1.4 g, 90% de rendimiento). EM (ESI) 300 $(M+Na)^+$

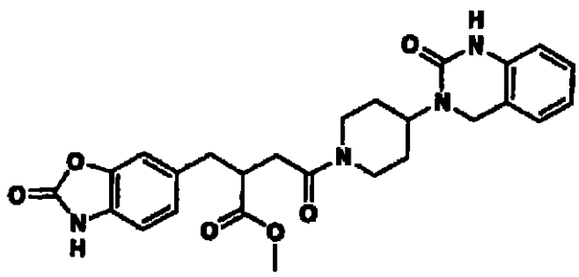
Éster de monometilo del ácido (±)-3-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-pentandioico



Preparado como se describió anteriormente por el éster de 1-metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-succínico (1.4 g, 99% de rendimiento). EM (ESI) 302 $(M+Na)^+$.

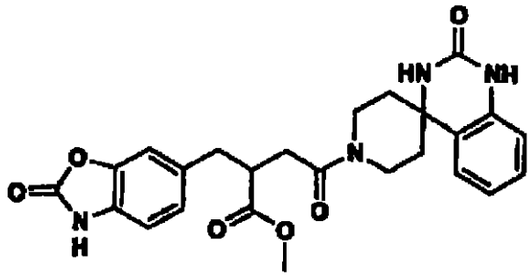
815

Éster de metilo del ácido (±)-4-oxo-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butírico



Preparado como se describió anteriormente por el éster de metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico EM (ESI) 493 $(MH)^+$.

Éster de metilo del ácido (±)-4-oxo-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butírico

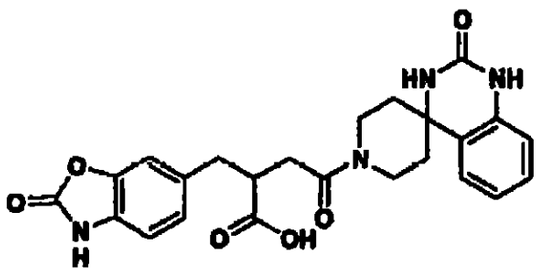


Preparado como se describió anteriormente por éster de metilo del ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-

817/816

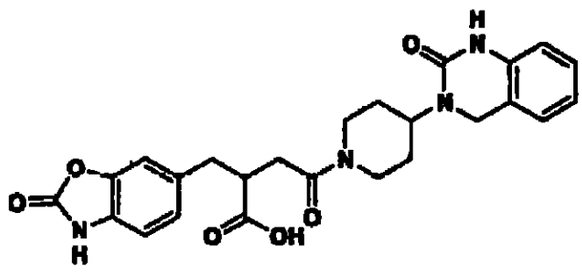
piperidinil]-butírico. EM (ESI) 479 $(MH)^+$.

Ácido (±)-4-oxo-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piridina-4,4'-quinazolina)]-butírico



Preparado como se describió anteriormente por el ácido -(±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico. EM (ESI) 465 $(MH)^+$.

Ácido (±)-4-oxo-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butírico

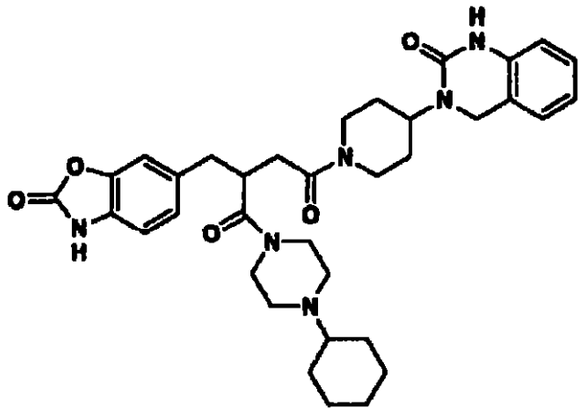


Preparado como se describió anteriormente por el ácido (±)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-

2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butírico. EM (ESI) 479 $(MH)^+$.

Ejemplo 256

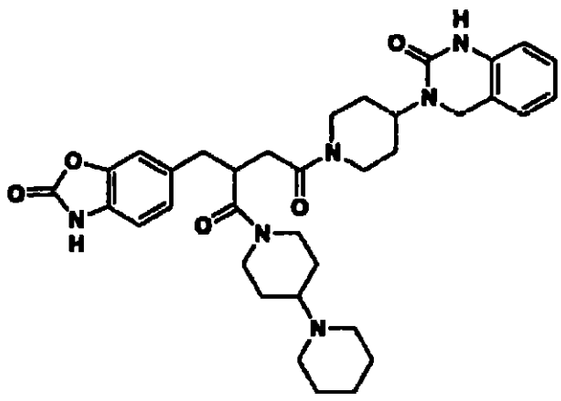
(±)-1-(4-ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butano-1,4-diona



Preparado como se describió anteriormente por la (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = 1.10 minutos, 629 $(MH)^+$.

Ejemplo 257

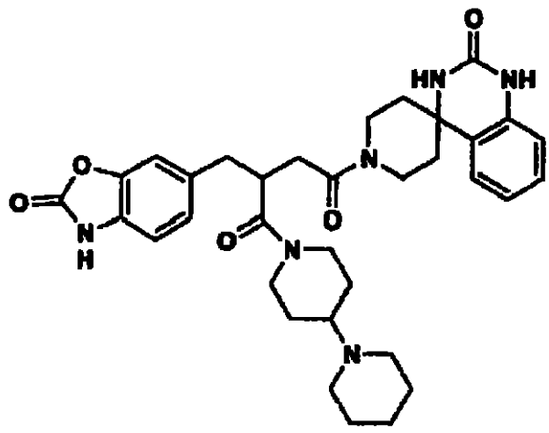
(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolina-3-il)-piperidin-1-il]-butano-1,4-diona



Preparado como se describió anteriormente por la (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,'4-piperidinil]-butano-1,4-diona. CL/EM: t_R =1.08 min, 629 $(MH)^+$. ^1H RMN (400 MHz, $CDCl_3$) δ 9.89 (1H, s), 8.28 (1H, d, J = 11.2 Hz), 6.90-7.25 (5H, m), 6.75 (1H, d, J = 8.0 Hz), 4.40-4.79 (3H, m), 4.35 (2H, s), 2.27-3.98 (19H, m), 1.46-2.10 (9H, m), 1.36 (1H, m), 1.08 (1H, m), 0.12 (1H, m).

Ejemplo 258

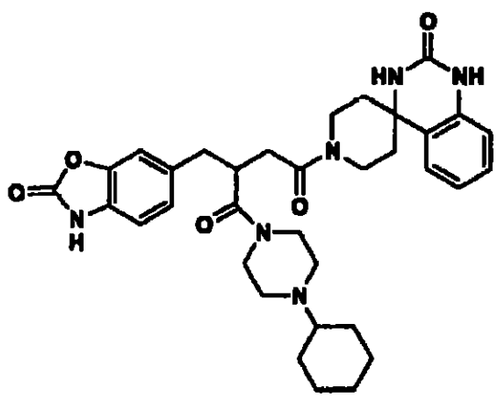
(±)-1-[1,4']bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona



Preparado como se describió anteriormente por la (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = 1.02 min, 615 $(MH)^+$.

Ejemplo 259

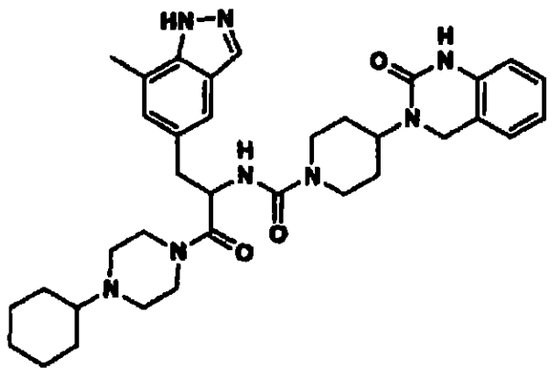
(±)-1-(4-ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona



Preparado como se describió anteriormente por la (±)-1-[1,4']bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[1'2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butano-1,4-diona. CL/EM: t_R = 1.04 min, 615 $(MH)^+$.

Ejemplo 260

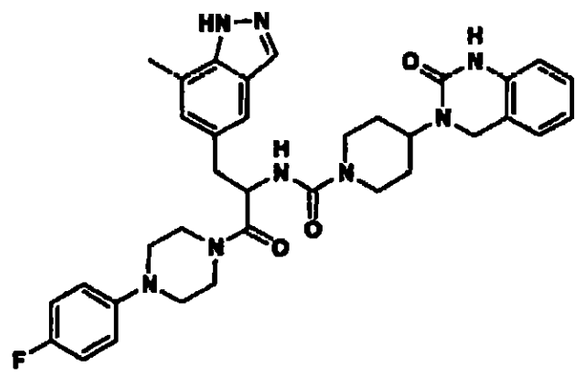
[2-(4-ciclohexil-piperazin-1-il)-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 16. ^{1}H-RMN (CD_3OD, 500 MHz) δ 0.81 (1H, m), 0.89 (1H, m), 1.02 (1H, m), 1.1-2.0 (12H, m), 2.23 (1H, d), 2.47 (1H, d), 2.61 (3H, s), 2.90 (4H, t), 3.08 (4H, m), 3.2-3.5 (4H, m), 3.82 (1H, m), 4.14 (2H, d), 4.29 (2H, s), 4.40 (1H, t), 6.80 (1H, d), 6.95 (1H, t), 7.12 (3H, m), 7.47 (1H, s), 8.01 (1H, s). Espectro de masa: 627.47 $(MH)^+$.

Ejemplo 261

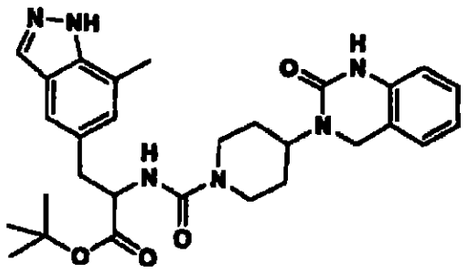
[2-[4-(4-fluoro-fenil)-piperazin-1-il]-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 2.34 min, 621.42 $(MH)^+$.

Ejemplo 262

Éster de tert-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



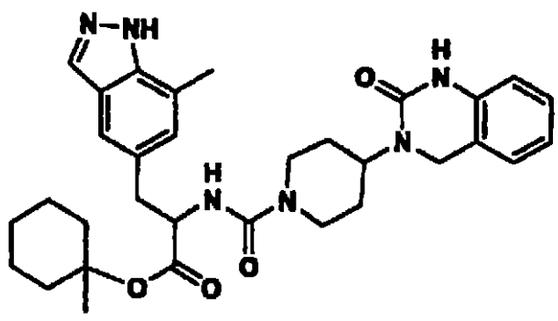
Una solución de ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

455 823

carbonil]-amino}-propiónico (50 mg, 0.105 mmol) y diciclohexilcarbodiimida (25 mg, 0.12 mmol) en dimetilformamida se agitó durante 30 minutos a temperatura ambiente, y luego pentafluorofenol (26 mg, 1.3 mmol) se agregó. La agitación se continuó a temperatura ambiente durante la noche, y luego el solvente se removió, el residuo se secó bajo alto vació durante 4 h. El éster de pentafluorofenilo crudo se usó sin purificación adiciona en la siguiente etapa. A una solución de alcohol tert-butílico (10 equiv.) en tetrahidrofurano a -78°C bajo nitrógeno se agregó 1.4M sec-butillitio en ciclohexano (10 equiv.). Después de 10-15 minutos, una solución de éster de pentafluorofenol (1 equiv.) en tetrahidrofurano se agregó. La mezcla de reacción se agitó a temperatura ambiente durante la noche. Los solventes se removieron in vacuo, y el residuo se purificó por CLAR preparativa para dar el compuesto deseado. ^{1}H-RMN (CD_3OD) δ 1.40 (s, 9H) 1.56 (m, 4H), 2.54 (s, 3H) 2.85 (m, 2H) 3.05 (m, 1H), 3.19 (m, 1H), 4.14 (m, 4H), 4.44 (m, 2H), 6.76 (d, J = 7.68 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.10 (m, 3H), 7.14 (s, 1H), 7.97 (s, 1H). CL/EM: t_R =2.19 minutos, 533.36 $(MH)^+$.

Ejemplo 263

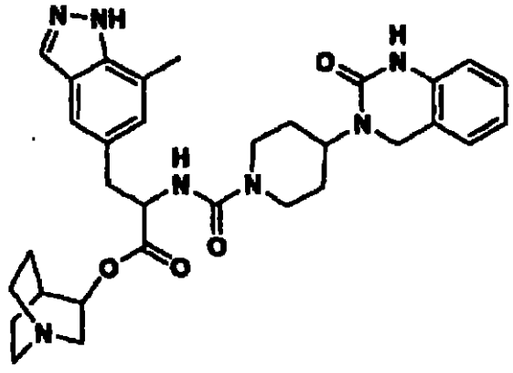
Éster de 1-metil ciclohexilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el éster de tert-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 2.47 minutos, 574.39 $(MH)^+$.

Ejemplo 264

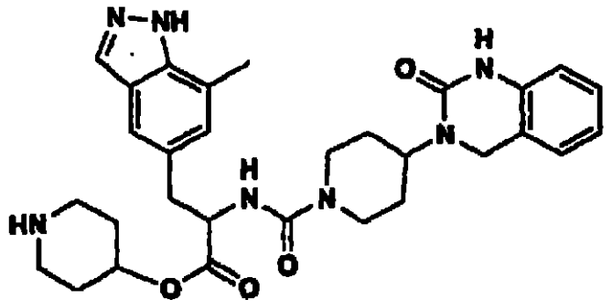
Éster de 1-aza-bicilo[2.2.2]oct-3-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



A una solución del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico (50 mg, 0.105 mmol), EDCI (100 mg), y 4-dimetilaminopiridina (0.2 equiv.) en dimetilformamida se agregó alcohol aza-biciclo[2.2.2]oct-3-ílico (0.525 mmol, 5 equiv.). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se removió in vacuo y el residuo se disolvió en acetato de etilo, se lavaron con salmuera, se secó sobre sulfato de magnesio, y se purificó por CLAR preparativa para proporcionar el compuesto deseado. CL/EM: t_R = 1.62 min, 586.41 $(MH)^+$.

Ejemplo 265

Éster de piperidin-4-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



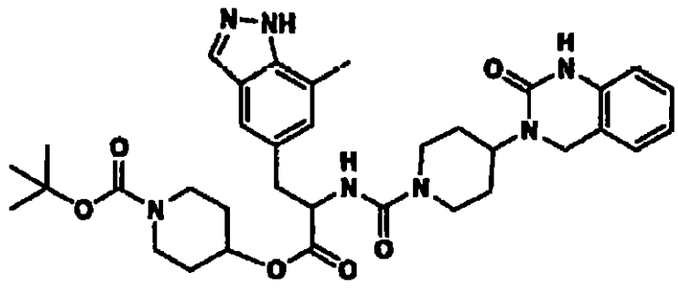
Preparado como se describió anteriormente por el éster de 1-aza-biciclo[2.2.2]oct-3-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 1.58

853/026

minutos, 560.37 $(MH)^+$.

Ejemplo 266

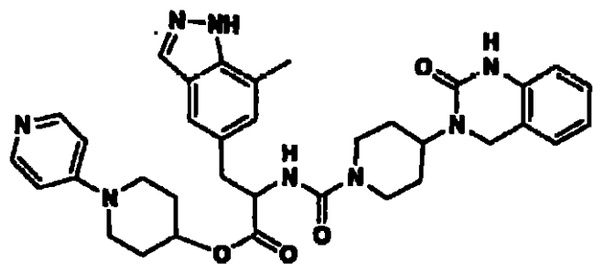
Éster de tert-butilo del ácido (±)-4-(3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propioniloxi)-piperidin-1-carboxílico



Preparado como se describió anteriormente por el éster de 1-aza-biciclo[2.2.2]oct-3-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 38 minutos, 660.42 $(MH)^+$.

Ejemplo 267

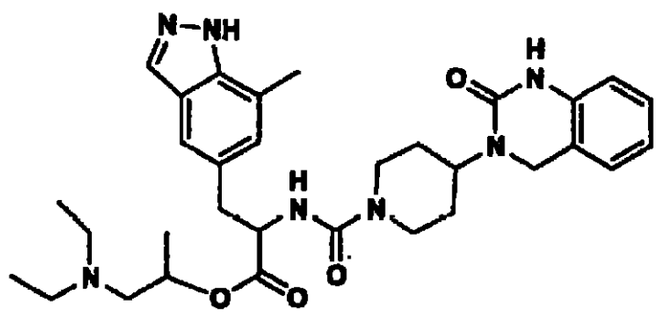
Éster de 3,4,5,6-tetrahidro-2H-[1,4']bipiridinil-4-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por éster de 1-aza-biciclo[2.2.2]oct-3-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 67 min, 637.43 $(MH)^+$.

Ejemplo 268

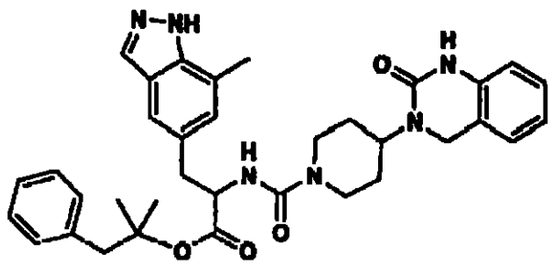
Éster de 1-dietilamino-1-metil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el éster de 1-aza-biciclo[2.2.2]oct-3-ilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 66 min, 590.44 $(MH)^+$.

Ejemplo 269

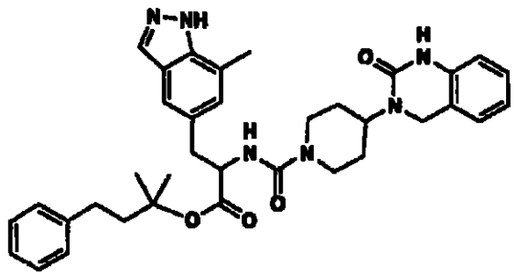
Éster de 1,1-dimetil-2-fenil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el éster de t-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 609.46 $(MH)^+$.

Ejemplo 270

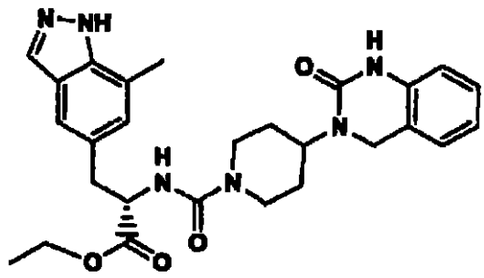
Éster de 1,1-dimetil-3-fenil-propilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por el éster

Ejemplo 271

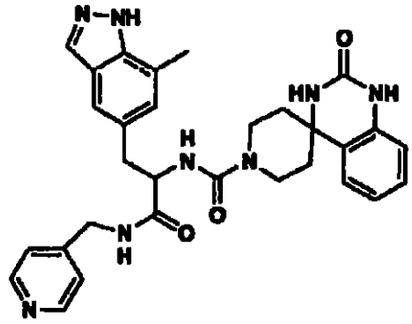
Éster de etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Preparado como se describió anteriormente por éster de t-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico. CL/EM: t_R = 1.98 minutos, 505.32 $(MH)^+$.

Ejemplo 272

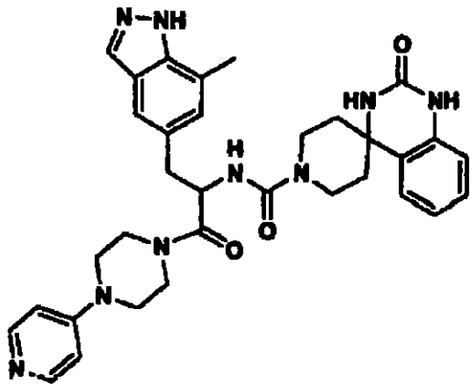
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-metil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 49 min, 553.12 $(MH)^+$.

Ejemplo 273

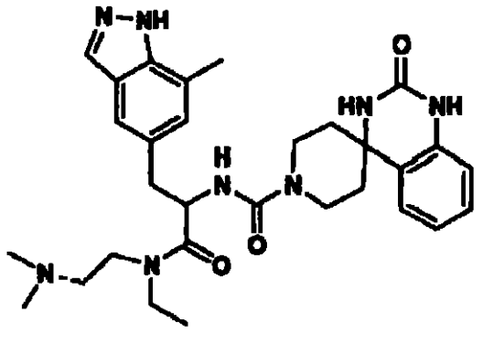
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-2'3'-dihidro-2'-oxoespiro}[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 56 min, 608.18 $(MH)^+$.

Ejemplo 274

(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[(2-dimetilamino-etil-etilcarbamoil)-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida

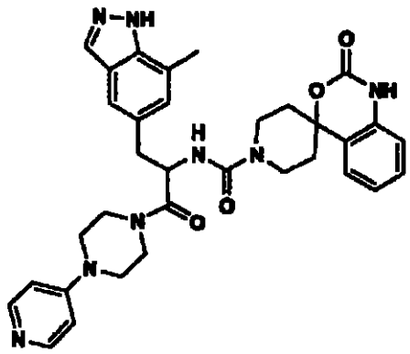


Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 1.58 min, 561.20 $(MH)^+$.

657 831

Ejemplo 275

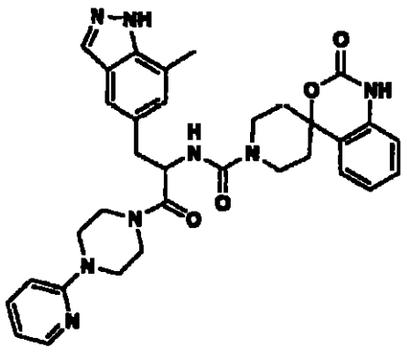
(±)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida



Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 1.56 min, 609.14 $(MH)^+$.

Ejemplo 276

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-2-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida



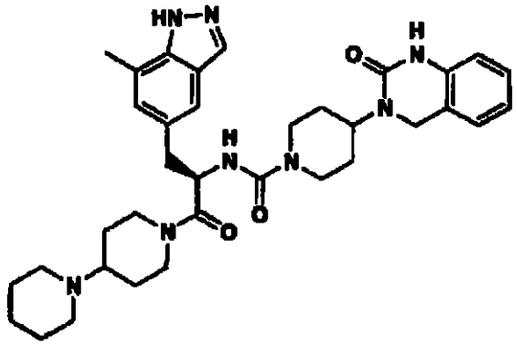
Preparado como se describió anteriormente por el ejemplo

832

16. CL/EM: 1.57 min, 609.17 $(MH)^+$.

Ejemplo 277

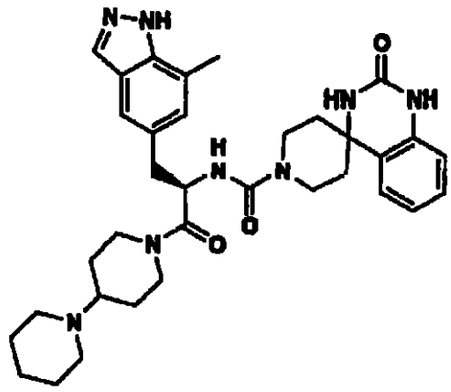
[2-[1,4']bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1d-carboxílico



Preparado como se describió anteriormente por el ejemplo 16. ^{1}H-RMN (CD_3OD, 500 MHz) δ -0.27 (1H, m), 0.75 (1H, m), 1.1-2.0 (12H, m), 2.10 (2H, m), 2.4-2.5 (3H, m), 2.57 (3H, s), 2.68 (2H, m), 2.92 (4H, m), 3.10 (4H, m), 3.9-5.1 (4H, varias m), 6.82 (1H, d), 6.96 (1H, t), 7.18 (3H, m), 7.50 (1H, s), 8.05 (1H, s). CL/EM: t_R = 1.68 min, 627.42 $(MH)^+$.

Ejemplo 278

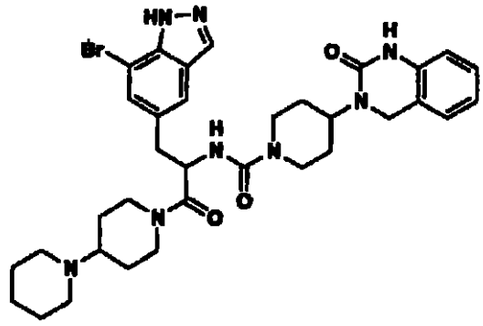
(R)-1-(7-metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2'3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida



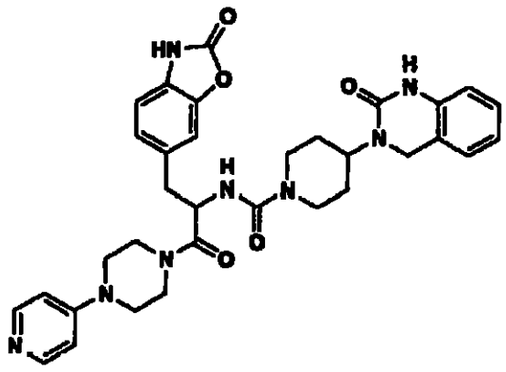
Preparado como se describió anteriormente por el ejemplo 16. CL/EM: t_R = 1.63 min, 613.36 $(MH)^+$.

Entre otros compuestos divisados dentro de la presente invención y capaces de hacerse de conformidad a la descripción proporcionada en la presente o aquellos métodos conocidos por aquellos de habilidad en el arte incluyen los siguientes ejemplos.

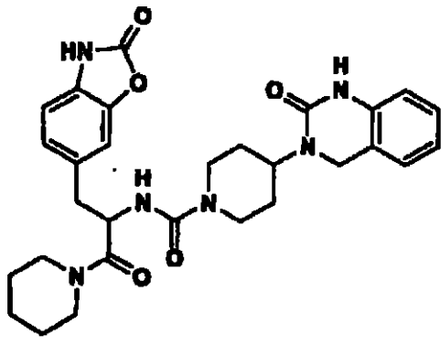
[2-[1,4']bipiperidinil-1'-il-1-(7-bromo-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



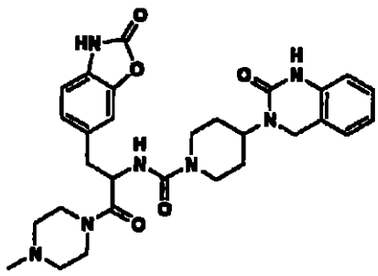
[2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-(4-piridin-4-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



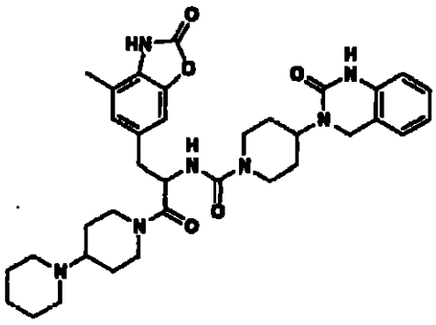
[2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



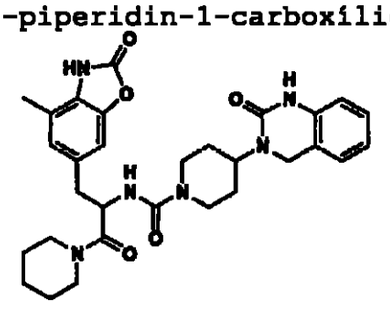
[2-(4-metil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



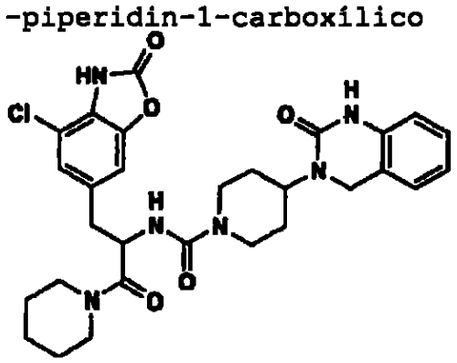
[2-[1,4']bipiperidinil-1'-il-1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



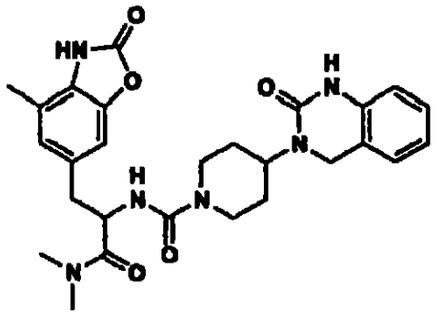
[1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



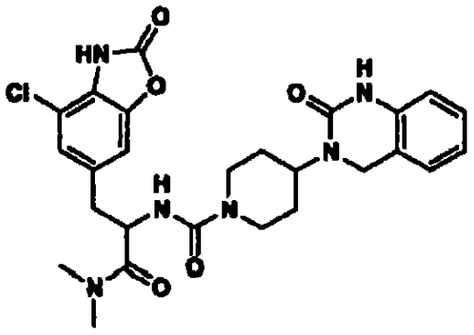
[1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



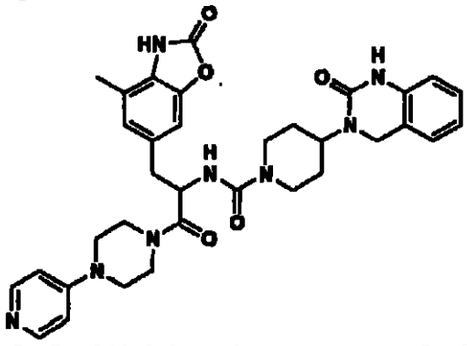
[1-dimetilcarbamoil-2-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



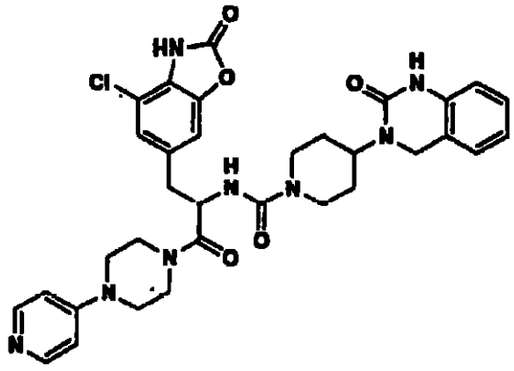
[2-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-1-dimetilcarbamoil-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



[1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

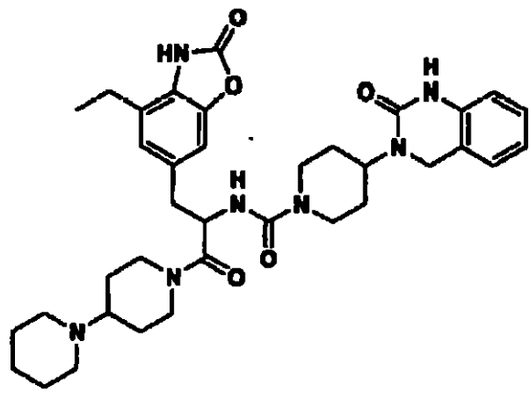


[1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H2-quinazolin-3-il)-piperidin-1-carboxílico

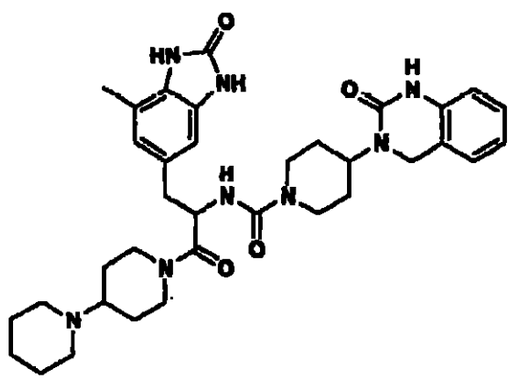


X57 838

[2-[1,4']bipiperidinil-1'-il-1-(4-etil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

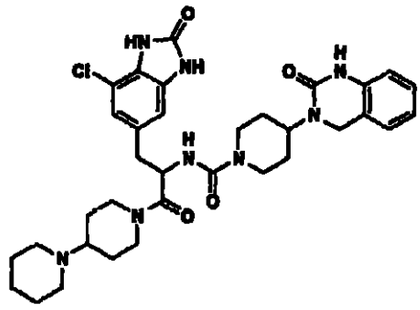


[2-[1,4']bipiperidinil-1'-il-1-(7-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

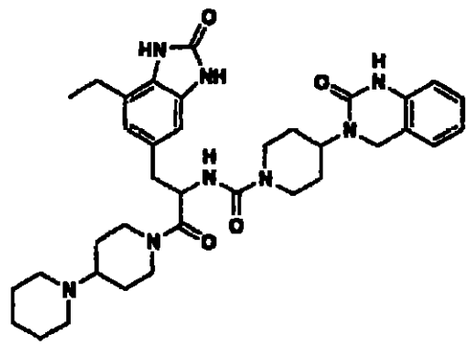


X65 839

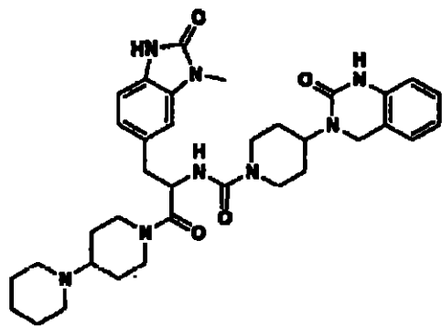
[2-[1,4']bipiperidnil-1'-il-1-(7-cloro-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



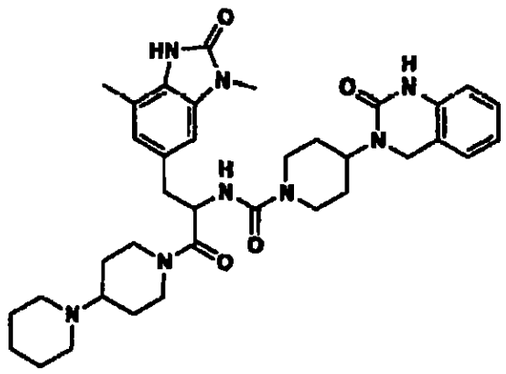
[2-[1,4']bipiperidinil-1'-il-1-(7-etil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



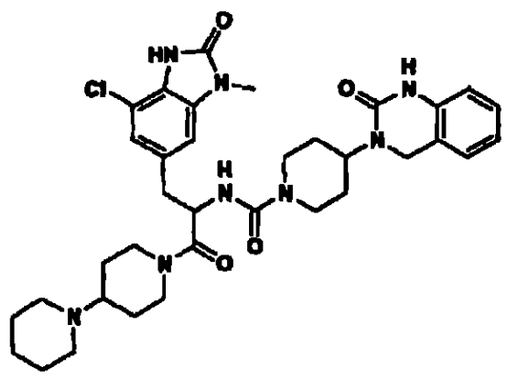
[2-[1,4']bipiperidinil-1'-il-1-(3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



[2-[1,4']bipiperidinil-1'-il-1-(3,7-dimetil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

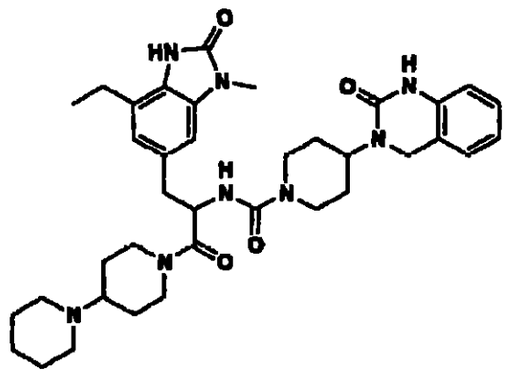


[2-[1,4']bipiperidinil-1'-il-1-(7-cloro-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico

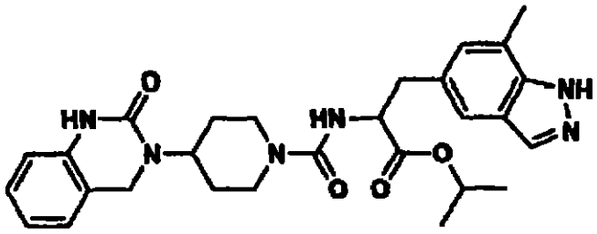


~~667~~ 841

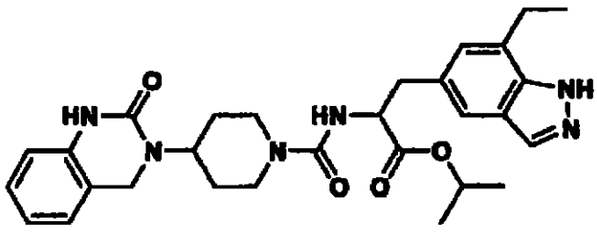
[2-[1,4']bipiperidinil-1'-il-1-(7-etil-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico



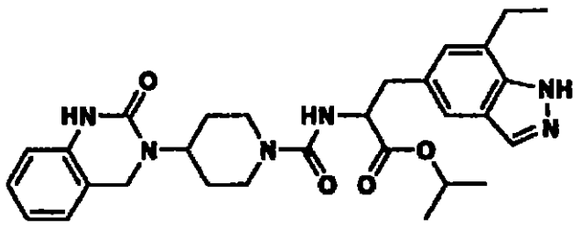
Éster de isopropilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



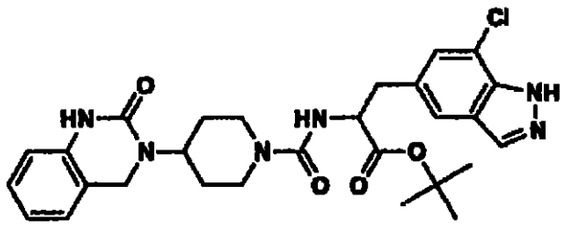
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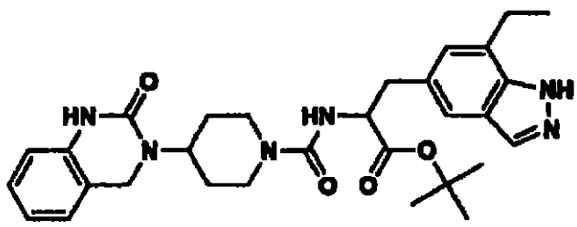
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Éster de tert-butilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico

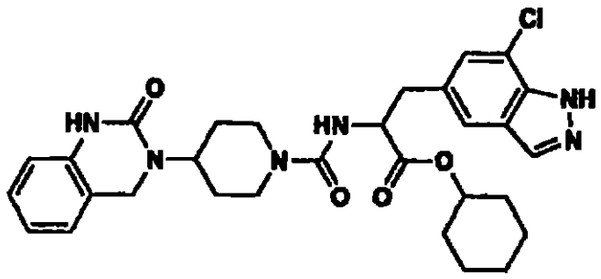


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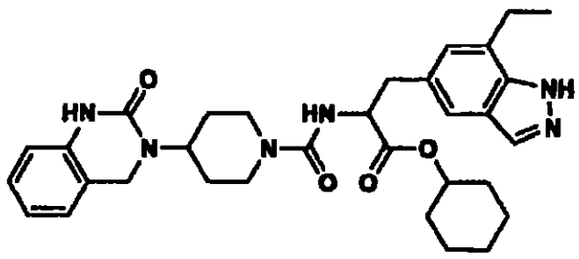


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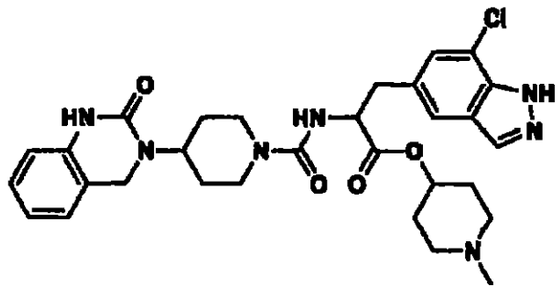
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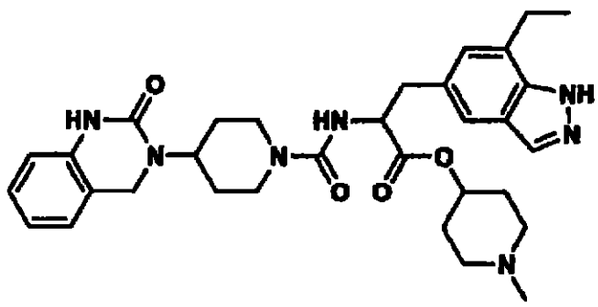
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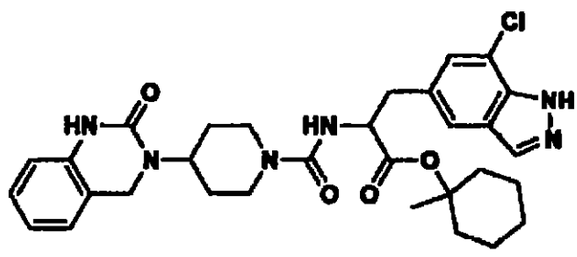
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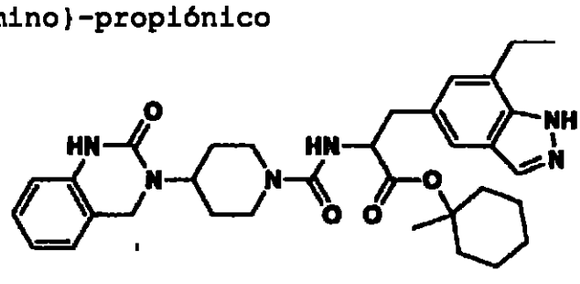
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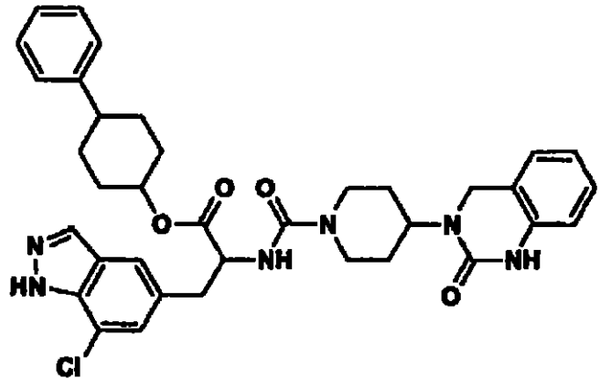
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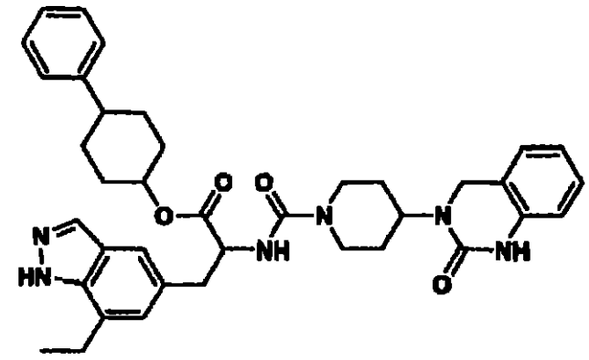
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Éster de 4-fenil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Éster de 4-fenil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico



Ensayo de enlace CGRP

Cultivo de tejido. Se hicieron crecer las células SK-N-MC a 37°C en CO_2 al 5% como una monocapa en un medio que consiste de MEM con sales Earle y L-glutamina (Gibco) completada con 10% de suero de bovino fetal (Gibco).

Peletizados celulares. Se enjuagaron dos veces las

células con solución salina amortiguada en fosfato (155 mM NaCl, 3.3 mM Na_2HPO_4, 1.1 mM KH_2PO_4, pH 7.4), y se incubaron por 5 a 10 minutos a 4°C en una solución amortiguadora hipotónica de lisis que consiste de 10 mM Tris (pH 7.4) y 5 mM EDTA. Las células se transfirieron de las placas a tubos de polipropileno (16 X 100 mm) y homogeneizaron usando un politron. Se centrifugaron los homogeneizados a 32,000 x g por 30 minutos. Se volvieron a suspender los peletizados en solución amortiguadora de lisis hipotónica fría con un cóctel inhibidor de proteasa de mamífero al 0.1% (Sigma) y se ensayaron para la concentración proteína. El homogeneizado SK-N-MC luego forma alícuotas y se almacenó a -80°C hasta que fue necesario.

Ensayo de enlace de radioligando. Los compuestos de la invención se solubilizaron y llevaron a través de diluciones en serie usando 100% DMSO. Las alícuotas de las diluciones en serie de los compuestos se diluyeron además 25 veces en solución amortiguadora de ensayo (50 mM Tris-Cl pH 7.5. 5 mM $MgCl_2$, 0.005% Triton X-100) y se transfirieron (volumen de 50 µl) en placas de ensayo de 96 pozos. [^{125}I]-CGRP (Amersham Biosciences) se diluyó hasta 60 pM en solución amortiguadora de ensayo y un volumen

de 50 µl se agregó a cada pozo. Los peletizados SK-N-MC se deshielaron, diluyeron en solución amortiguadora de ensayo con un cóctel inhibidor de proteasa de mamífero fresco al 0.1% (Sigma) y se homogeneizaron nuevamente. El homogeneizado de SK-N-MC (5µg/pozos) se agregó en un volumen de 100 µl. Las placas de ensayo luego se incubaron a temperatura ambiente por 2 h. Se detuvieron los ensayos por la adición de solución amortiguadora de lavado fría en exceso (20 mM Tris-Cl pH 7.5, 0.1% BSA) inmediatamente por filtración sobre filtro de fibra de vidrio (Whatman GF/B) previamente sumergidos en 0.5% PEI. Se definió el enlace no específico con 1 µM beta-CGRP. Se determinó la radioactividad unida a la proteína usando un contador gamma o de escintilación. El IC_{50} se definió como la concentración de un compuesto de la invención requerida para desplazar 50% de enlace de radioligando.

En la tabla de abajo, los resultados se anotaron como sigue: A ≤ 10 nM; 10 nM < B ≤ 100 nM; 100 nM < C ≤ 1000 nM; D < 1000 nM.

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Tabla 4. Enlace CGRP, función cAMP y datos de la arteria cerebral humana Ex Vivo

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
1	C	*	*
2	A	A	A
3	B	B	B
4	B	B	*
5	A	A	*
6	A	A	A
7	C	C	*
8	C	C	*
9	B	B	*
10	C	B	*
11	B	B	*
12	B	C	*
13	C	*	*
14	D	*	*
15	C	C	*

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Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
16	A	A	A
17	A	A	A
18	A	B	A
19	A	A	A
20	A	A	A
21	A	A	A
22	A	A	*
23	A	A	A
24	B	B	*
25	A	A	A
26	B	B	*
27	B	C	*
28	C	*	*
29	A	*	*
30	B	*	*
31	A	A	*
32	C	*	*
33	C	*	*
34	A	A	*
35	B	B	*
36	B	B	*

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850

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
37	A	B	*
38	B	B	*
39	C	C	*
40a	A	A	*
40b	B	*	*
40c	D	*	*
40d	C	*	*
40e	D	*	*
40f	D	*	*
40g	D	*	*
40h	D	*	*
40i	B	*	*
40j	D	*	*
40k	D	*	*
41a	B	*	*
41b	A	*	*
41c	A	*	*
41d	B	*	*
41e	A	*	*
41f	B	*	*
42	C	*	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
43	A	A	A
44	C	*	*
45	A	*	*
46	B	B	*
47	A	A	A
48	D	*	*
49	A	*	*
50	A	*	*
51	D	*	*
52	d	*	*
53	D	*	*
54	B	C	A
55	C	*	*
56	A	A	*
57	C	*	*
58	D	*	*
59	C	*	*
60	C	*	*
61	C	C	*
62	B	B	*
63	C	C	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
64	B	*	B
65	A	B	B
66	C	*	*
67	B	C	B
68	A	A	A
69	A	A	A
70	A	A	A
71	A	A	A
72	A	A	A
73	B	B	*
74	A	A	A
75	A	B	*
76	B	B	A
77	B	B	*
78	A	A	*
79	B	C	*
80	C	*	*
81	B	C	*
82	B	C	*
83	B	C	*
84	B	B	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
85	C	*	*
86	C	B	C
87	B	B	*
88	C	B	*
89	C	B	*
90	B	*	*
91	C	*	*
92	B	C	*
93	C	*	*
94	C	C	*
95	C	*	*
96	D	*	*
97	D	*	*
98	D	*	*
99	D	D	*
100	C	*	*
101	D	*	*
102	C	*	*
103	C	*	*
104	C	*	*
105	C	*	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
106	C	*	*
107	C	*	*
108	C	*	*
109	C	*	*
110	C	*	*
111	C	*	*
112	C	*	*
113	C	*	*
114	c	*	*
115	C	*	*
116	C	*	*
117	C	*	*
118	C	*	*
119	C	*	*
120	C	*	*
121	C	*	*
122	C	*	*
123	B	*	*
124	C	*	*
125	C	*	*
126	C	*	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
127	C	*	*
128	C	*	*
129	C	*	*
130	C	*	*
131	C	*	*
132	C	*	*
133	C	*	*
134	C	*	*
135	C	*	*
136	C	*	*
137	C	*	*
138	C	*	*
139	C	*	*
140	B	*	*
141	C	*	*
142	C	*	*
143	C	*	*
144	C	*	*
145	C	*	*
146	B	*	*
147	C	*	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
148	B	*	*
149	B	*	*
150	B	*	*
151	C	*	*
152	C	*	*
153	C	*	*
154	C	*	*
155	C	*	*
156	C	*	*
157	C	*	*
158	B	*	*
159	B	*	*
160	C	*	*
161	B	*	*
162	C	*	*
163	C	*	*
164	C	*	*
165	C	*	*
166	C	*	*
167	C	*	*
168	C	*	*

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Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
169	C	*	*
170	C	*	*
171	B	*	*
172	B	*	*
173	C	*	*
174	C	*	*
175	C	*	*
176	B	*	*
177	B	*	*
178	B	*	*
179	C	*	*
180	C	*	*
181	C	*	*
182	C	*	*
183	C	*	*
184	B	*	*
185	C	*	*
186	C	*	*
187	C	*	*
188	C	*	*
189	C	*	*

Ejemplo #	CGRP de enlace[1] IC_{50} (nM)	Función[2] cAMP IC_{50} (nM)	Arteria[3] cerebral EC_{50} (nM)
190	C	*	*
191	C	*	*
192	C	*	*
193	B	*	*
194	C	*	*
195	C	*	*
196	B	*	*
197	C	*	*
198	C	*	*
199	B	*	*
200	B	*	*
201	C	*	*

Ensayo cíclico AMP

Antagonismo funcional. El antagonismo de los compuestos de la invención se determinó al medir la formación del AMP cíclico (monofosfato 3'5' cíclico de adenosina) células SK-N-MC que expresan endógenamente el receptor humano CGRP. Se acopla el complejo del receptor CGRP con la proteína Gs, y el enlace CGRP a este complejo conduce al AMP cíclico por medio de la activación dependiente de Gs de una adenilato ciclasa (Juaneda C et al., TiPS, 2000; 21:432-438; incorporada aquí como

referencia). Consecuentemente los antagonistas del receptor CGRP inhiben la formación AMP cíclica en inducida por CGRP en células SK-N-MC (Doods H et al., Br J Pharmacol, 2000; 129 (3); 420-423); incorporada aquí como referencia). Para las mediciones cíclicas de AMP, se incubaron células SK-N-MC con 0.3 nM CGRP solo o en presencia de diversas concentraciones de los compuestos de la invención por 30 minutos a temperatura ambiente. Se preincubaron los compuestos de la invención con células SK-N-MC por 15 minutos antes de la adición de CGRP para permitir la adición del receptor (Edvinsson et al., Eur J Pharmacol, 2001, 415:39-44; incorporada aquí como referencia). Se extrajo el AMP cíclico usando el reactivo de lisis y se determino la concentración por un inmunoensayo usando un kit de ensayo por separación por exclusión directa cAMP SPA (Amersham Pharmacia Biotech). Se calcularon los valores IC50 usando un ajuste en Excel. Se determinaron los compuestos probados de la invención por ser antagonistas ya que mostraron una inhibición dependiente de la dosis de la producción AMP cíclica inducida por CGRP. Ver la tabla 3 para resumen de los resultados.

Análisis Schild. Se puede usar el análisis Schild para caracterizar la naturaleza del antagonismo de los compuestos de la invención. La respuesta de dosis de la producción de cAMP estimulada por CGRP se genera con CGRP o en presencia de diversa composiciones de loas compuestos de la invención. La dosis de antagonista se gráfica como X contra la relación de

dosis (definida como IC50 del agonista con presencia de los compuestos dividida por el IC50 del agonista solo) menos 1 como Y). Luego se efectuó la regresión lineal con el eje X e Y transformado en logaritmo. Una pendiente que no difiere significativamente de la unidad 1 indica un antagonismo competitivo. K_b es la constante de disociación del antagonismo.

Tabla 5 Análisis Schild.

Ejemplo #	K_b(nM)	Traslape
2	0.16	0.94
3	55	0.96
5	3	0.92
6	0.36	0.93
16		1.03
17	1.1	0.92
18	1	0.8
21	0.018	0.89
43	0.018	1.2
45		1.4
47	0.1	0.93
69	0.016	1
70		0.71
71	2	0.87

Ver figura 1. Análisis Schild.

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Ensayo De Arteria Cerebral Humana Ex Vivo

Razonamiento e Introducción. Para suministrar una evidencia directa de la capacidad de los compuestos novedosos para invertir la dilatación inducida por CRPG en los vasos cerebrales humanos, se diseñó un ensayo ex vivo. Brevemente, se montaron anillos de vasos aislados en un baño de tejido en donde los vasos se contrajeron previamente con cloruro de potasio (KCI) y se dilataron completamente con hCGRP, luego se invirtió esta relajación por la adición acumulada de antagonistas del receptor CGRP (siguen los detalles completos).

Muestras de tejido. Se obtuvieron muestras de autopsias de muestras humanas de vendedores (ABS Inc. o NDRI) se transportaron todos los vasos sobre una solución amortiguadora HEPES enfriada con hielo (composición en mM: NaCl 130, KCl 4, KH2PO4 1.2, MgSO4 1.2, CaC12 1.8, Glucosa 6, NaHCO3 4, HEPES 10, EDTA 0.025). Al recibirse, los vasos se colocaron en una solución amortiguadora fría de Kreb (composición en mM: NaCl 118.4, KCl 4.7, KH2PO4 1.2, MgSO4 1.2, CaC12 1.8, Glucosa 10.1 NaHCO3 25) saturada con carbógeno (5% CO2 y 95% de oxígeno).

Baños de tejido aislado. Se limpiaron los vasos de tejido conectivos y se cortaron en segmentos cilíndricos de 4-5 mm de longitud. Luego se montaron los vasos en baño de tejido entre dos ganchos de acero inoxidable, uno de los

cuales se fijó y el otro del cual se conectó a un transductor de desplazamiento de fuerza. La tensión del vaso se registró continuamente usando un sistema de adquisición de datos (Powerlab, AD Instruments, Mountain View, CA) conectado al transductor. Los baños de tejido que contienen solución amortiguadora Krebs y los vasos montados fueron controlados por temperatura (37°C) y pH (7.4) con un burbujeo continuo de carbógeno. Se dejaron equilibrar los segmentos de arterias por alrededor de 30-45 min hasta que se alcanzó un tono de reposo estable. Previo al ensayo se cebaron los vasos (acondicionados), con 100mM KCl y se lavaron posteriormente. Los vasos se pre-contrajeron con 10 mM KCl y se dilataron completamente con 1 nM hCGRP. Las curvas de respuesta a la concentración a los antagonistas del receptor CGRP se efectuaron por la adición acumulativa de fármacos en unidades medias logarítmicas en vasos completamente dilatados. A cada concentración, se expresaron los efectos de los fármacos como porcentaje de la inversión de la relajación inducida por CGRP en cada vaso. Se efectuaron el análisis de datos y ensayo actual para cada vaso individualmente, ajustando los datos de respuesta a la concentración a una función logística de cuatro parámetros por un análisis de regresión lineal para estimar los valores EC50. Se suministra un resumen de resultado en la Tabla 3.

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Método no terminal para evaluar la eficacia in vivo de antagonistas del receptor CGRP de molécula pequeña en mamíferos

Introducción. El bloqueo de la dilatación de la arteria cerebral inducido por el péptido relacionado con el gen de calcitonina (CGRP) se ha propuesto como un tratamiento para el dolor de cabeza por migraña, sin embargo, los antagonistas del receptor CGRP novedosos de molécula pequeña han mostrado diferencias específicas de especies con una actividad relativamente pobre en roedores (Mallee et al. J Biol Chem 2002 277:14294) requiriendo nuevos modelos para la evaluación de la eficacia in vivo. Los primates no humanos (por ejemplo, los titíes) son los únicos animales que se conocen que tiene una farmacología del receptor CGRP similar a la del humano, otorgada por la presencia de un residuo específico de aminoácidos (Trp74) en su secuencia RAMP1 que es responsable del fenotipo del receptor humano (Mallee et al. J. Biol Chem 2002 277:14294). Ya que los modelos actuales de migraña utilizan principalmente ratas (Escott et al. Brain Res 1995 669:93; Williamson et al. Cephalalgia 1997 17:525), o son invasores, los procedimientos terminales en primates (Doods et al. Br J Pharmacol 2000 129:420), un modelo de supervivencia no invasivo novedoso en primates no humanos para la evaluación de la eficacia in vivo de los antagonistas del receptor CGRP como en la presente invención es una

contribución importante. Aunque se sabe que la activación trigémina incrementa el flujo sanguíneo facial y cerebral (Goadsby & Edvinsson, 1993) (Doods et al., 2000) la demostración de la relación directa entre el flujo sanguíneo facial y la dilatación de la arteria cerebral efectuada en los mismos animales no se conocía. Por lo tanto, antes de iniciar los estudios en primates no humanos, la medición Doppler con láser del flujo sanguíneo facial se validó directamente en la rata como un substituto para la dilatación de la arteria cerebral en estudios terminales que midieron el diámetro de la arteria cerebral y los cambios en el flujo sanguíneo facial en los mismos animales (ver figura 2. Validación directa del flujo sanguíneo facial como substituto para la dilatación de la arteria cerebral en las ratas). En ambas mediciones, se indujeron incrementos comparables por i.v CGRP y se bloquearon por el antagonista péptido hαCGRP(8-37). Después el método de cambios inducidos por i.v CGRP en el flujo sanguíneo facial se valido como un modelo de recuperación en ratas anestesiadas con isoflurano utilizando hαCGRP(8-37). El método de supervivencia luego se estableció en primates no humanos y un estudio de respuesta de dosis que caracteriza la actividad de i.v CGRP se finalizo (ver figura 3. Respuesta de dosis para hαCRGP en el flujo sanguíneo facial con láser Doppler de primates no humanos). Los

antagonistas del receptor hαCRGP de molécula pequeña y los péptidos se usaron para validar el modelo de primates no humanos. El pretratamiento con antagonistas de molécula pequeña o hαCRGP(8-37) que depende de la dosis, inhibieron los incrementos estimulados por CGRP intravenoso en el flujo sanguíneo facial de primates (ver figura 4. Inhibición de los cambios inducidos por CGRP en el flujo sanguíneo facial de primate no humano), sin alterar la presión de la sangre (ver figura 5. Efecto de el antagonista CGRP en la presión sanguínea de primates no humanos). El tratamiento posterior de antagonista también invierte los incrementos inducidos por CGRP en el flujo sanguíneo facial (no se muestra). Este modelo de supervivencia proporciona un procedimiento de recuperación no invasivo novedoso para evaluar los efectos abortivos y profilácticos de los antagonistas del receptor CGRP en primates no humanos o en animales transgénicos con PAMP1 (Trp74) que tiene una farmacología del receptor CGRP como un marcador substituto para la actividad del diámetro del vaso cerebral.

Animales. Los titíes comunes hembra y macho adultos (Callithrix jacchus) adquiridos con Harlan y que pesan 350-550 g sirvieron como sujetos. Otros mamíferos que expresan endógenamente RAMP1 que tienen Trp 74 o mamíferos transgénicos con un RAMP1 humanizado que tiene Trp74 también se pueden emplear en el método aquí

descrito.

Anestesia y preparación quirúrgica. Se anestesian los animales por inhalación con isoflurano en una cámara de inducción (4-5% de inducción rápida mantenida con 1-2.5% Solomon et al., 1999). Se mantiene la anestesia al suministrar un suministro constante de aire y oxígeno (50:50) e isoflurano por medio de una máscara facial o por entubación y ventilación (con monitoreo de gas sanguíneo). Se mantiene la temperatura de la sangre a 38±0.5°C por colocación en una superficie controlada con temperatura automatizada con un sonda rectal. Un área pequeña de pelo (aproximadamente 1.5 cm cuadrados) se retira de uno o ambos lados de la cara por aplicación de una crema depilatoria y/o afeitado. Se sujetaron las áreas quirúrgicas y se separaron con betadina. Se colocó una línea intravenosa en cualquier vena accesible para la administración de los compuestos de prueba y el agonista de sector CGRP y se fuera necesario el retiro de las muestras de sangre (máximo de 2.5 ml, 10%) para un monitoreo de gas en la sangre y análisis de contenido. Se administró una solución de dextrosa al 5% intravenosa con objeto de mantener los niveles de azúcar en la sangre. Se observó la profundidad de la anestesia al medir la presión sanguínea y el pulso cardiaco usando un método de sujeción del brazo no invasivo y un medidor de oxígeno de pulso respectivamente. La guanetidina 5-10 mg/kg i.v. complementada con 5 mg/kg i.v

como se necesita se puede dar para estabilizar el flujo pico en un flujo de sangre facial observado con cambios repetidos inducidos por la estimulación en el flujo de sangre (Escott et al., 1999; incorporado como referencia en la presente). Se observa el flujo de sangre microvascular al colocar una sonda de flujo Doppler láser autoadhesiva a la piel facial.

Administración del compuesto. Los compuestos de prueba se pueden administrar i.v.(0.01-5 ml/kg), i.m. (0.01-0.5 ml/kg), s.c. (0.01-5ml/kg) o p.o. (0.1-10ml/kg) (Diehl et al., 2001; incorporado como referencia en la presente). Los agonistas del receptor CGRP se puede suministrar i.v. (0.01-5 ml/kg), i.d. (10-100µl/sitio) o s.c. (10-100 µl/sitio).

Flujometría Doppler Láser. Un incremento de control en el flujo sanguíneo facial se induce por la administración de un vasodilatador tal como CGRP (0.05-100 µg/kg i.v.) o 2-20 pmol/sitio i.d) o adrenomedulina (ADM, 0.05-5 mg/kg i.v. o 10-100 pmol/sitio i.d.). El compuesto de prueba o vehículo se administra antes (pretratamiento) o después (post-tratamiento) de la administración repetida al agente vasodilatador, suministrando la capacidad de evaluar acciones profilácticas o terapéuticas. Se observa la presión sanguínea continuamente para asegurar una profundidad adecuada de la anestesia, y se ajusta el anestésico para mantener niveles estables que coincidan con los valores de pretratamiento. Durante la recolección de los datos de flujometría Doppler de

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láser se puede reducir el isoflurano hasta 0.215-0.75% como los estudios electrofisiológicos previos en titíes encontraron que los registros fueron sensibles a la concentración de isoflurano (Solomon, 1999 incorporado como referencia en al presente). Para reducir el número de animales usados, el efecto del compuesto de prueba en los cambios inducidos por el vasodilatador intravenoso en el flujo sanguíneo se puede repetir tres veces en una sección sencilla.

Recuperación. Se regresaron los animales a la jaula de transporte que se coloca en una superficie controlada por temperatura, para mantener calientes a los animales hasta que están completamente despiertos y circulando. Se puede probar los animales después de 7 a 14 días de reposo, y se pueden probar repetidamente intervalos de 7 a 14 días dependiendo de la salud del animal.

Ver Diehl KH, R, Morton D, Pfister R, Rabemampianina Y, Smith D, Vidal JM, van de Vorstenbosch C. A good practice guide to the administration of substances and removal of blood, including routes and volumes. J Appl Toxicol. 2001 Jan Feb; 2 (1): 15-23; Doods H, Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Pharmacologial profile of BIBN4096BS, the first selective small molecule CGRP-receptor antagonist. Br J Pharmacol. 2000 Feb; 129(3): 4250-3; Edvinsson L. Calcitonin gene-

related peptide (CGRP) and the pathophysiology of headache: therapeutic implications. CNS Drugs 2001; 15(10): 745-53; Escott KJ, Beattie DT, Connor HE, Brain SD. Trigeminal ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide. Brain Res. 1995 Jan 9;669(1):93-9; Goadsby PJ. Edvinsson L. The trigeminovascular system and migrain: studies characterizing cerecrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 1993 Jan; 33(1):48-56; Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olsen J. CGRP may play a causative role in migraine. Cephalalgia, 2002, 22, 54-61; Mallee JJ, Salvatore CA, LeBourdelles B, Oliver KR, Longmore J, Koblan KS, Kane SA. RAMP1 determines the species selectivity of non-peptide CGRP receptor antagonists. J. Biol Chem. 2002 Feb 14 [pub. Por adelantado a impresión]; Solomon SG, White AJ.Martin PR. Temporal contrast sensitivity in the lateral geniculate nucleus of a New World monkey, the marmoset Callithrix jacchus. J Physiol. 1999 Jun 15;517 (Pt 3): 907-17; todos incorporados como referencia en la presente.

Alejamiento de otros modelos de migraña. Esta invención representa un modelo novedoso de migraña y es notablemente diferente de otros niveles de migraña. Algunas de las características que hacen diferencia del

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método de la presente invención incluyen (i) único modelo de supervivencia de migraña en cualquier especie; (ii) el único modelo para demostrar los efectos abortivos (posteriores al tratamiento) de los antagonistas CGRP en incrementos inducidos activos en el flujo sangre; (iii) la única demostración de una relación directa entre un flujo sanguíneo facial y la dilatación de la arteria intracraneal efectuada en los mismo animales; (iv) el único modelo para utilizar técnicas quirúrgicas no invasoras y no requiere colocación de catéter, entubación o bloqueo neuromuscular, (v) el único modelo de primates para usar el CGRP exógeno como el estímulo y demostrar el bloqueo de pretratamiento por antagonismo de CGRP y una invasión del postratamiento por antagonismo de CGRP (vi) el único modelo de migraña para usar anestesia de isoflurano en animales que respiran espontáneamente. Los modelos descritos en Williamson et al., Sumatriptan, inhiben la vasodilatación neurogénica de los vasos sanguíneos durales en estudios con microscopio intravital en ratas anestesiadas. Cephalalgia. 1997 Jun; 17(4):525-31; Williamson DJ, Hargreaves RJ, Hill RG Spheard SL. Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide in dural vessel diameter in the anaesthetized rat. Cephalalgia. 1997 Jun, 17(4): 518-24; Escott KJ et al., Trigeminal

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ganglion stimulation increases facial skin blood flow in the rat: a major role for calcitonin gene-related peptide. Brain Res. 1995 Jan 9;669(1):93-9; Chu DQ et al., The calcitonin gene-related peptide (CGRP) antagonist CGRP(8-37) blocks vasodilatation in inflamed rat skin: involvement of adrenomedullin in addition to CGRP. Neurosci Lett. 2001 Sep 14; 310(2-3): 169-72; Escott KJ, Brain SD. Effect of a calcitonin gene-related peptide antagonist (CGRP 8-37) on skin vasodilatation and oedema induced by stimulation of the rat saphenous nerve. Br J Pharmacol. 1993 Oct; 110(2): 772-6; Hall JM, Simey L, Lippton H, Hyman A, Kang-Chang J. Brain SD. Interaction of human adrenomedullin 13-52 with calcitonin gene-related peptide receptors in the microvascular of the rat and hamster. Br J Pharmacol. 1995 Feb; 114(3): 592-7; Hall JM, Brain SD. Interaction of amuylin with calcitonin gene-related peptide receptors in the microvasculature of the hamster cheek pouch in vivo. Br J Pharmacol. 1999 Jan; 126(1): 280-4; and Doods H. Hallermayer G, Wu D, Entzeroth M, Rudolf K, Engel W, Eberlein W. Pharmacological profile of BIBN4096BS, the firs selective small molecule CGRP receptor antagonist. Br J Pharmacol. 2000 Feb; 129(3): 420-3 fallan al poseer las características notables del método de la presente invención.

En la tabla a continuación los resultados se indican

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como siguen W ≤ 25%; 25% < X ≤ 50%; 50% < Y ≤ 75%; Z > 75%.

Tabla 6. Inhibición del incremento inducido por CGRP en flujo sanguíneo facial Doppler con láser en un primate no humano (por ejemplo, Titi común).

Primate no humano (% de inhibición) de incremento inducido por CGRP (10 µg/kg. iv) en flujo sanguíneo facial Doppler láser					
Ejemplo #	0.01 mg/kg iv	0.03 mg/kg iv	0.1 mg/kg iv	0.3 mg/kg iv	1 mg/kg, iv
2	W	X	X	Y	Z
6					Z
16		Y			
69		Y	Z		
HαCGRP (8-37)					Z
	W < 25%; 25% < X < 50%; 50% < Y < 75%; Z > 75%.				

Ver Figura 5. Efecto del Antagonista CGRP en la presión sanguínea del primate no humano.

Se hace constar que con esta fecha, el mejor método conocido por la solicitante para llevar a cabo la práctica la citada invención, es el que resulta claro de la presente descripción de la invención.

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Reivindicaciones

Habiéndose descrito la invención como antecede, se reclama como propiedad lo contenido en las siguientes reivindicaciones.

1. Un compuesto, caracterizado porque es seleccionado del grupo que consiste de éster de metilo del ácido (±)-3-(3-Ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1-(3-ciano-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(3-ciano-7-metil-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-3-(7-isopropil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1(7-isopropil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-metil-1H-indazol-5-il-

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metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-3-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-2-[4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-3-(7-metil-1H-indazol-5-il)-propiónico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(2-oxo-1,2,4,5-tetrahidro-benzo[d][1,3]diazepin-3-il-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-Hidroxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-metoxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-cloro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

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(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-7,7-dimetil-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-indazol-5-il)propanoato de (±)-metilo;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-fenilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(4-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-

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il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(2-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-o-tolilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

2-(4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-etil-3-metil-1H-indazol-5-il)propanoato de (±)-metilo;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-8'-fluoro-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

N-((R)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-

(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-1-(dimetilcarbamoil)-2-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(1,2-Dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo;

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N((R)-1-(dimetilcarbamoil)-2-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(2',3'-dihidro-2'-oxoespiro(piperidin-4,4'-(1H)-quinazolina)carboxamida;

4-(1,2-dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-((R)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

[2-(4-Ciclohexil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

carboxílico;

[2-(4-Isopropil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-

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oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

[2-[1,4']Bipiperidinil-1'-il-1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butiramida;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-

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ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida;

N'-(2-(7-Metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiril)-hidrazida del ácido (±)-fenil-acético;

(±)-1-[1,4']Bipiperidinil-1'-il-4-[4-(8-fluoro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-2-(7-metil-1H-indazol-5-ilmetil)-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina]-butano-1,4-diona;

(±)-1-(4-Ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

(±)-1-(4-Ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

[2-(4-Ciclohexil-piperazin-1-il)-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-

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dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[4-(4-Fluoro-fenil)-piperazin-1-il]-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de tert-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo de 1-metilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-aza-biciclo[2.2.2]oct-3-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de piperidin-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido (±)-4-(3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propioniloxi)-piperidin-1-carboxílico;

Éster de 3,4,5,6-tetrahidro-2H-[1,4']bipiridinil-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-dietilamino-1-metil-etilo del ácido (±)-3-(7-

metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1,1-dimetil-2-fenil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1,1-dimetil-3-fenil-propilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de etilo del ácido (±)-3-(7-Metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-metil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[(2-dimetilamino-etil-etil carbamoil)-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-(1-piridin-2-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-(4H-3',1-

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benzoxazina-4,4'-piperidina]-1-carboxamida;

[2-(1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1d-carboxílico; y

(R)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida o una sal o solvato farmacéuticamente aceptable del mismo.

2. Un compuesto, caracterizado porque es seleccionado del grupo que consiste de [2-[1,4']bipiperidinil-1'-il-1-(7-bromo-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Metil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

carboxílico;

[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-Dimetilcarbamoil-2-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-1-dimetilcarbamoil-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-etil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

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[2-[1,4']Bipiperidinil-1'-il-1-(7-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(3,7-dimetil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-3-metil-2-oxo-

2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de isopropilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-cloro-1H-

indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 4-fenil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico; y

Éster de 4-fenil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico o una sal o solvato farmacéuticamente aceptable del mismo.

3. Una composición farmacéutica caracterizada porque comprende un compuesto seleccionado del grupo que consiste de

Éster de metilo del ácido (±)-3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1-(3-ciano-1H-indol-5-il-

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metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(3-ciano-7-metil-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-3-(7-isopropil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1(7-isopropil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-3-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-2-[4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-3-(7-metil-1H-indazol-5-il)-propiónico;

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{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(2-oxo-1,2,4,5-tetrahidro-benzo(d)[1,3]diazepin-3-il-1-carboxílico;

{2-(1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-hidroxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-metoxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-cloro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-7,7-dimetil-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-indazol-5-il)propanoato de (±)-metilo;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-fenilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(4-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(2-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-o-tolilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

2-(4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-etil-3-metil-1H-indazol-5-il)propanoato de (±)-metilo;

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(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-8'-fluoro-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

N-((R)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-1-(Dimetilcarbamoil)-2-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo;

N-((R)-3-(2,3-Dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-

dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-1-(dimetilcarbamoil)-2-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(2',3'-dihidro-2'-oxoespiro(piperidin-4,4'-(1H)-quinazolina)carboxamida;

4-(1,2-Dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-((R)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

[2-(4-Ciclohexil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Isopropil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(R)-N-((R)-3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-

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1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

[2-[1,4']Bipiperidinil-1'-il-1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']bipiperidinil-1'-il-1-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-bromo-2-oxo-2,3-

dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']bipiperidinil-1'-il-1-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butiramida;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida;

N'-{2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiril}-hidrazida del ácido (±)-fenil-acético;

(±)-1-[1,4']Bipiperidinil-1'-il-4-[4-(8-fluoro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-2-(7-metil-1H-indazol-5-ilmetil)-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-

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quinazolina]-butano-1,4-diona;

(±)-1-(4-Ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

(±)-1-(4-ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

[2-(4-Ciclohexil-piperazin-1-il)-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[4-(4-Fluoro-fenil)-piperazin-1-il]-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de tert-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil ciclohexilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

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Éster de 1-aza-biciclo[2.2.2]oct-3-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de piperidin-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido (±)-4-(3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propioniloxi)-piperidin-1-carboxílico;

Éster de 3,4,5,6-tetrahidro-2H-[1,4']bipiridinil-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-dietilamino-1-metil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1,1-dimetil-2-fenil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1,1-dimetil-3-fenil-propilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

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carbonil]-amino}-propiónico;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-metil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[(2-dimetilamino-etil-etil carbamoil)-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-2-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida;

[2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1d-carboxílico; y

(R)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida o una sal o solvato farmacéuticamente aceptable del mismo.

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4. Una composición farmacéutica caracterizada porque comprende un compuesto seleccionado del grupo que consiste de

[2-[1,4']Bipiperidinil-1'-il-1-(7-bromo-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Metil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-Dimetilcarbamoil-2-(4-metil-2-oxo-2,3-dihidro-

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benzooxazol-6-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-1-dimetilcarbamoil-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-etil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-Oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(3,7-dimetil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de isopropilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-

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carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 4-fenil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico; y

Éster de 4-fenil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico o una sal o solvato farmacéuticamente aceptable del mismo.

5. El uso de un compuesto seleccionado del grupo que consiste de

Éster de metilo del ácido (±)-3-(3-ciano-1H-indol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1-(3-ciano-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(3-ciano-7-metil-1H-indol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-3-(7-isopropil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

[2-[1,4']Bipiperidinil-1'-il-1(7-isopropil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1(7-etil-3-metil-1H-indazol-5-il-metil)-2-oxo-etil]-amida del ácido (±)-4-(2,2-dioxo-1,4-dihidro-2H-2λ^6-benzo[1,2,6]tiadiazin-3-il)-piperidin-1-carboxílico;

Éster de metilo del ácido (±)-2-[4-(6-Ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino]-3-(7-metil-1H-indazol-5-il)-propiónico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(6-ciano-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-(1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(2-oxo-1,2,4,5-tetrahidro-benzo(d](1,3]diazepin-3-il-1-carboxílico;

{2-(1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il

metil)-2-oxo-etil}-amida del ácido (±)-4-(6-hidroxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-(1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-metoxi-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

{2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-il metil)-2-oxo-etil}-amida del ácido (±)-4-(8-cloro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Etil-1H-indazol-5-il)-1-(6,7-dihidro-7,7-dimetil-1H-pirazolo[4,3-c]piridin-5(4H)-il)-1-oxopropan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-metil-1H-indazol-5-

il)propanoato de (±)-metilo;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-fenilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(4-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(1-(4-(2-fluorofenil)piperazin-1-il)-3-(7-metil-1H-indazol-5-il)-1-oxopropan-2-il)piperidin-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-o-tolilpiperazin-1-il)propan-2-il)piperidin-1-carboxamida;

2-(4-(8-Fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(7-etil-3-metil-1H-indazol-5-il)propanoato de (±)-metilo;

(±)-N-(3-(7-Etil-3-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(R)-N-((R)3-(2-oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(8-fluoro-

1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

(±)-N-(3-(7-Metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-8'-fluoro-2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)-1-carboxamida;

(±)-4-(8-Fluoro-1,2-dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-(3-(7-metil-1H-indazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

N-((R)-3-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-1-(dimetilcarbamoil)-2-(2-(trifluorometil)-1H-benzo[d]imidazol-5-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

2-(4-(1,2-Dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamido)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)propanoato de (R)-metilo;

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-1-(dimetilcarbamoil)-2-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)etil)-4-(1,2-dihidro-2-oxoquinazolin-3(4H)-il)piperidin-1-carboxamida;

N-((R)-3-(2,3-dihidro-2-oxo-1H-benzo[d]imidazol-6-il)-1-

oxo-1(4-piperidin-1-il)piperidin-1-il)propan-2-il)-4-(2',3'-dihidro-2'-oxoespiro(piperidin-4,4'-(1H)-quinazolina)carboxamida;

4-(1,2-Dihidro-2,4-dioxoquinazolin-3(4H)-il)-N-((R)-3-(7-metil-1H-benzo[d][1,2,3]triazol-5-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)piperidin-1-carboxamida;

[2-(4-Ciclohexil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Isopropil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-

oxoespiro-(piperidin-4,4'-1H-benzo[d][1,3]oxazina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(piperidin-1-il)piperidin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(ciclohex-1-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

(R)-N-((R)-3-(2-Oxo-2,3-dihidro-benzooxazol-6-il)-1-oxo-1-(4-(prop-2-il)piperazin-1-il)propan-2-il)-2,4-dihidro-2'-oxoespiro-(piperidin-4,4'-1H-quinazolina)-1-carboxamida;

[2-[1,4']Bipiperidinil-1'-il-1-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(5-cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(5-bromo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido

(R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-yodo-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidinil]-butiramida;

(±)-N-(1-Bencil-2-hidroxi-etil)-2-(7-metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiramida;

N'-(2-(7-Metil-1H-indazol-5-ilmetil)-4-oxo-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butiril}-hidrazida del ácido (±)-fenil-acético;

(±)-1-[1,4']Bipiperidinil-1'-il-4-[4-(8-fluoro-2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-2-(7-metil-1H-indazol-5-ilmetil)-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(7-metil-1H-indazol-5-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina]-butano-1,4-diona;

(±)-1-(4-Ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-

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benzooxazol-6-ilmetil)-4-[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-il]-butano-1,4-diona;

(±)-1-[1,4']Bipiperidinil-1'-il-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

(±)-1-(4-Ciclohexil-piperazin-1-il)-2-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-4-[2',3'-dihidro-2'-oxoespiro-(piperidin-4,4'-quinazolina)]-butano-1,4-diona;

[2-(4-Ciclohexil-piperazin-1-il)-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[4-(4-Fluoro-fenil)-piperazin-1-il]-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido (±)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de tert-butilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil ciclohexilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-aza-biciclo[2.2.2]oct-3-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de piperidin-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-

piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido (±)-4-(3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propioniloxi)-piperidin-1-carboxílico;

Éster de 3,4,5,6-Tetrahidro-2H-[1,4']bipiridinil-4-il del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-dietilamino-1-metil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

1,1-Dimetil-2-fenil-etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

1,1-Dimetil-3-fenil-propilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de etilo del ácido (±)-3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-metil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-

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piperazinil]-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[(2-dimetilamino-etil-etil carbamoil)-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-4-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida;

(±)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1-piridin-2-il-piperazinil]-2-oxoetil]-1',2'-dihidro-2'-oxoespiro-[4H-3',1-benzoxazina-4,4'-piperidina]-1-carboxamida;

[2-[1,4']Bipiperidinil-1'-il-1-(7-metil-1H-indazol-5-ilmetil)-2-oxo-etil]amida del ácido (R)-4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1d-carboxílico; y

(R)-1-(7-Metil-1H-indazol-5-ilmetil)-2-[1,4-bipiperidin]-1-il-2-oxoetil]-2',3'-dihidro-2'-oxoespiro-[piperidin-4,4'-(1H)-quinazolina]-1-carboxamida o una sal o solvato farmacéuticamente aceptable del mismo en la manufactura de un medicamento para el tratamiento o prevención de migraña.

6. El uso de un compuesto seleccionado del grupo que consiste de

[2-[1,4']Bipiperidinil-1'-il-1-(7-bromo-1H-indazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-

quinazolin-3-il)-piperidin-1-carboxílico;

[2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-Oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-Metil-piperazin-1-il)-2-oxo-1-(2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-piperidin-1-il-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-Dimetilcarbamoil-2-(4-metil-2-oxo-2,3-dihidro-benzooxazol-6-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-(4-cloro-2-oxo-2,3-dihidro-benzooxazol-6-il)-1-dimetilcarbamoil-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-

2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Metil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[1-(4-Cloro-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-2-(4-piridin-4-il-piperazin-1-il)-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(4-etil-2-oxo-2,3-dihidro-benzooxazol-6-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

947 915

[2-[1,4']Bipiperidinil-1'-il-1-(3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(3,7-dimetil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-cloro-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

[2-[1,4']Bipiperidinil-1'-il-1-(7-etil-3-metil-2-oxo-2,3-dihidro-1H-benzoimidazol-5-ilmetil)-2-oxo-etil]-amida del ácido 4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carboxílico;

Éster de isopropilo del ácido 3-(7-metil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de isopropilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

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Éster de tert-butilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de tert-butilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-piperidin-4-il del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-cloro-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 1-metil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico;

Éster de 4-fenil-ciclohexilo del ácido 3-(7-cloro-1H-

94F917

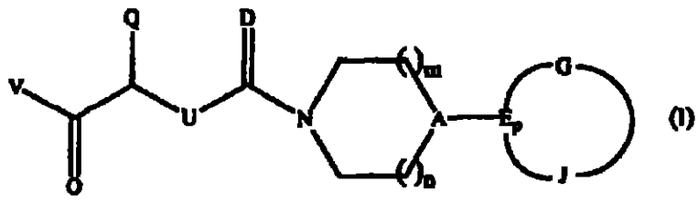
indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico; y

Éster de 4-fenil-ciclohexilo del ácido 3-(7-etil-1H-indazol-5-il)-2-{[4-(2-oxo-1,4-dihidro-2H-quinazolin-3-il)-piperidin-1-carbonil]-amino}-propiónico o una sal o solvato farmacéuticamente aceptable de los mismos en la manufactura de un medicamento para el tratamiento o prevención de migraña.

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Resumen de la Invención

La presente invención se refiere a compuestos de la Fórmula (I)



(I)

como antagonistas de los receptores péptidos relacionados con el gen de calcitonina ("receptor CGRP"), composiciones farmacéuticas que los comprenden, métodos para su identificación, métodos de tratamiento que los usan y su uso en terapia para tratamiento de la vasodilatación neurogénica, inflamación neurogénica, migraña, y otros dolores de cabeza, lesión térmica, choque circulatorio, sofocaciones asociadas con la menopausia, enfermedades inflamatorias de las vías aéreas tales como asma y enfermedad pulmonar obstructiva crónica (COPD por sus siglas en inglés) y otras condiciones, el tratamiento de las cuales se puede efectuar por el antagonismo de los receptores CGRP.

FIGURA 1

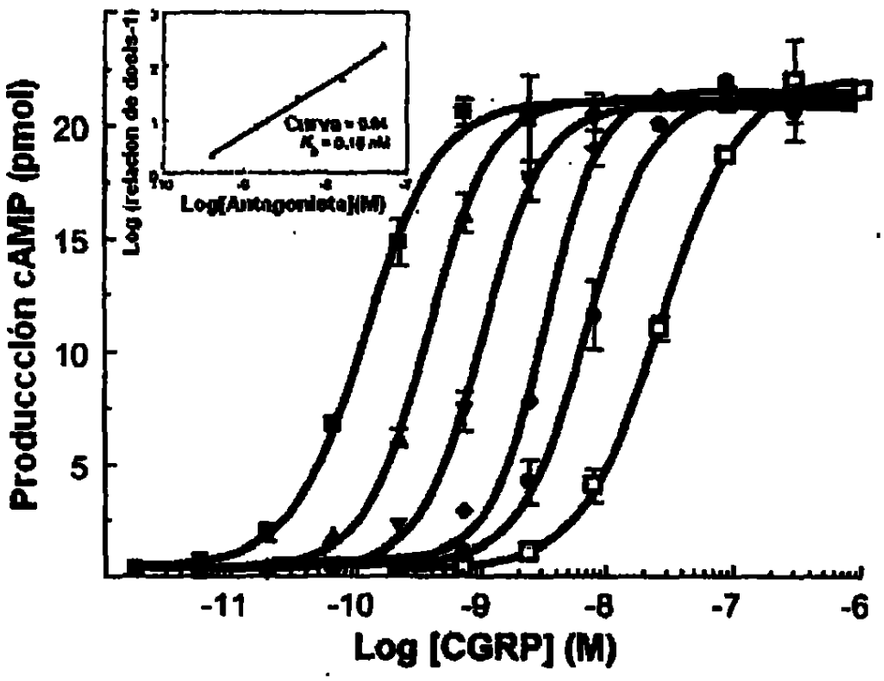

Producccción cAMP (pmol)
20
15
10
5
-11
-10
-9
-8
-7
-6
Log [CGRP] (M)
Log (relación de dosis-1)
Log[Antagonista](M)

FIGURA 2

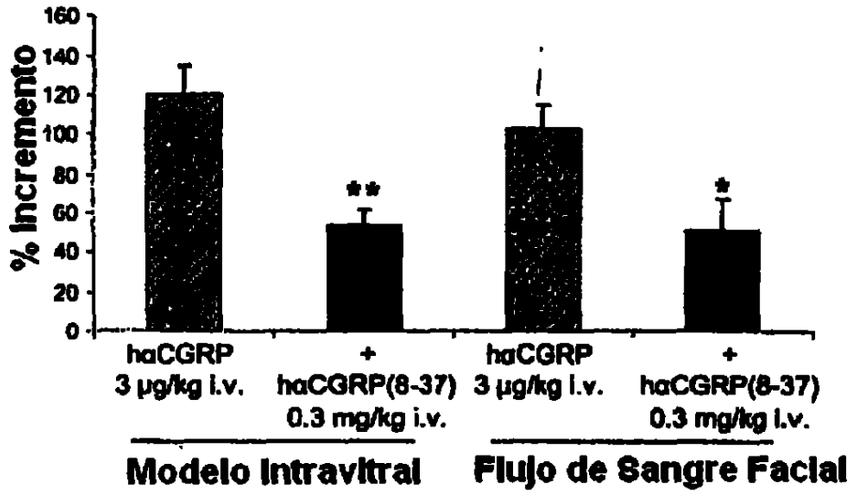

% incremento
160
140
120
100
80
60
40
20
0
**
*
haCGRP
3 µg/kg i.v.
+
haCGRP(8-37)
0.3 mg/kg i.v.
haCGRP
3 µg/kg i.v.
+
haCGRP(8-37)
0.3 mg/kg i.v.
Modelo Intravital
Flujo de Sangre Facial

FIGURA 3

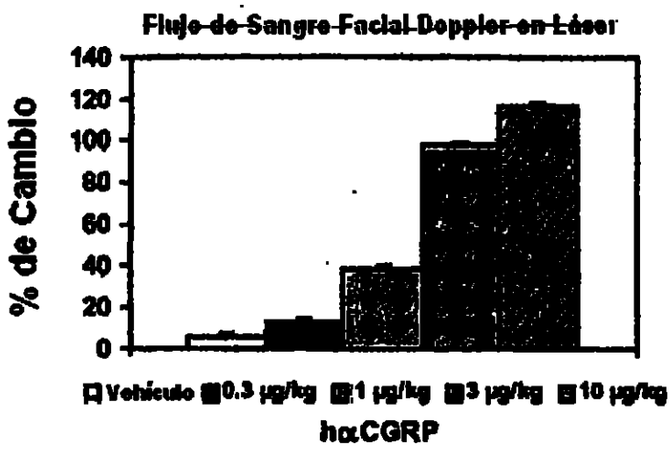

Flujo de Sangre Facial Doppler en Láser
% de Cambio
140
120
100
80
60
40
20
0
Vehículo
0.3 µg/kg
1 µg/kg
3 µg/kg
10 µg/kg
hαCGRP

FIGURA 4

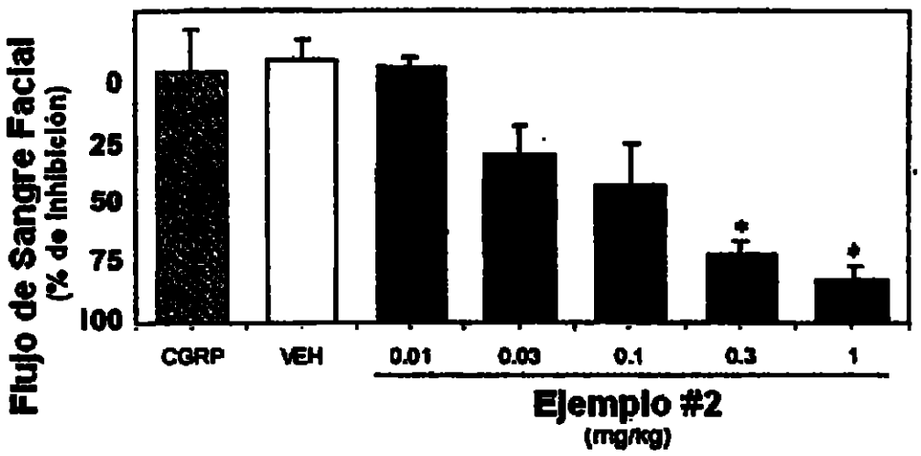
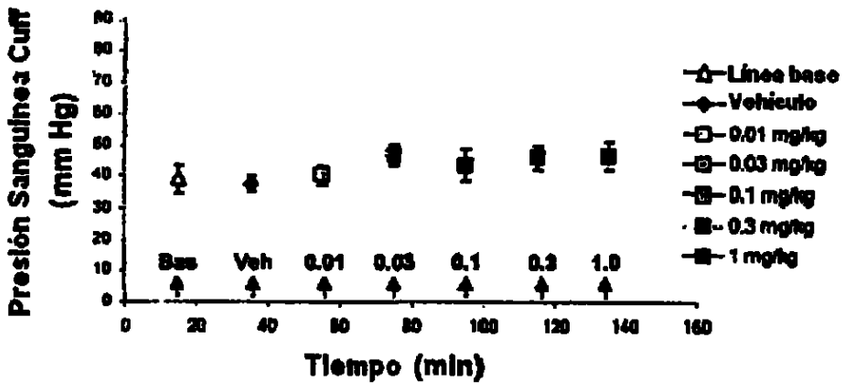

Flujo de Sangre Facial
(% de Inhibición)
0
25
50
75
100
CGRP
VEH
0.01
0.03
0.1
0.3
1
Ejemplo #2
(mg/kg)

FIGURA 5


Presión Sanguínea Cuff (mm Hg)
Tiempo (min)
Bas
Veh
0.01
0.03
0.1
0.3
1.0
Línea base
Vehículo
0.01 mg/kg
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg

10135 - WO-RCT
(related to CT2777) 9/24
105's filed in U.S.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SHAH MAKUJINA
BRISTOL-MYERS SQUIBB COMPANY
P.O.BOX 4000
PRINCETON, NJ 08543-4000

PCT

MAKUJINA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Ma.

	Date of Mailing (day/month/year) 30 AUG 2004
Applicant's or agent's file reference 10135PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US03/38799	International filing date (day/month/year) 05 December 2003 (05.12.2003)
Applicant BRISTOL-MYERS SQUIBB COMPANY	

SEP 15 2004

1. ☒ The applicant is hereby notified that the international search report has been established and is 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, Facsimile No.: (41-22) 740.14.35

   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 is 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 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.

   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 ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer [illegible] Telephone No. (703) 872-1600

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BMS PATENT LAW
AUG 31 2004

Docketed Item US-CT277(NF) - 105 - 11/30/04
Due Date US-CT2777(CIP1) - 105 - 11/30/04
Attorney _____

Form PCT/ISA/220 (April 2002) (See notes on accompanying sheet)

ETS 925

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10125PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US03/38799	International filing date (day/month/year) 05 December 2003 (05.12.2003)	(Earliest) Priority Date (day/month/year)
Applicant BRISTOL-MYERS SQUIBB COMPANY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant. ☐ None of the figures
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/38799

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61P 25/00; A61K 31/535, 31/52, 31/55, 31/54, 31/495, 31/50; C07D 239/00, 243/10, 265/00, 285/00
US CL : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/11128 A1 (DR. KARL THOMAE G.M.B.H.) 19 March 1998, see Example No. 576, 580, 587, etc.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2004 (24.08.2004)	30 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Joseph Brusca Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/38799

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61P 25/06; A61K 31/535, 31/52, 31/55, 31/54, 31/495, 31/50; C07D 239/00, 243/10, 265/00, 285/00
US CL : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/11128 A1 (DR. KARL THOMAE G.M.B.H.) 19 March 1998, see Example No. 576, 580, 587, etc.	1-6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
24 August 2004 (24.08.2004)

Date of mailing of the international search report
30 AUG 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Brenda Coleman
Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

9/75 9/20

TRATADO DE COOPERACION EN MATERIA DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL
(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia al expediente del solicitante o del mandatario	PARA ACCION ADICIONAL	ver Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior
10135PCT		
No. de solicitud internacional	Fecha de presentación internacional (día/mes/año)	(Fecha de Prioridad) (La más cercana) (día/mes/año)
PCT/US03/38799	05 Diciembre 2003 (05.12.2003)	04 de Agosto 2003 (04.08.2003)
Solicitante		
BRISTO-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18. Se transmite una copia a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 2 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte.

1. **Bases del reporte.**

a. Con respecto al idioma, la búsqueda internacional se ha llevado a cabo en base a la solicitud internacional en el lenguage en el que se presentó, salvo que se indique lo contrario bajo este punto.

☐ La búsqueda internacional se ha llevado a cabo en base a la traducción de la solicitud internacional presentada a esta autoridad (Regla 23.1(b)).

b. Con respecto a cualquier secuencia de aminoácido y/o nucleótido descrito en la solicitud internacional, el reporte internacional se llevó a cabo en base al listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional en forma leible en computadora.

☐ presentada posteriormente a esta Autoridad en forma escrita

☐ presentada posteriormente a esta Autoridad en forma leible en computadora

☐ la declaración de que el listado de secuencia presentado posteriormente no va más allá de la descripción en la solicitud internaiconal como se presentó.

☐ la declaración de que la información registrada en la forma leible en computadora es idéntica al listado de secuencia escrito que se ha presentado

2. ☐ **Ciertas reivindicaciones no son localizables** (ver el Cuadro I).

3. ☐ **La unidad de la invención es deficiente** (ver el Cuadro II).

4. Con respecto al título,

☒ el texto se aprueba tal como lo presentó el solicitante,

☐ Esta Autoridad ha establecido que el texto sea como sigue:

5. Con respecto al resumen,

☒ El texto se aprueba tal como lo presentó el solicitante.

☐ Esta Autoridad ha establecido el texto, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro III. El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcional comentarios a esta autoridad.

6. La figura de los dibujos que se va a publicar con el resumen es la Figura No. _____

☐ como lo sugirió el solicitante. ☐ Ninguna de las figuras

☐ porque al solicitante le faltó sugerir una figura.

☐ Porque esta figura caracteriza mejor la invención.

REPORTE DE BUSQUEDA INTERNACIONAL

No. de Solicitud Internacional
PCT /US03/38799

A. CLASIFICACION DEL ASUNTO RELACIONADO
IPC (7) : A 61P 25/08; A61K 31/535, 31/52, 31/55, 31/54, 31/495, 31/50; C07D 239/00, 243/10, 265/00, 285/00
US CL: 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

De acuerdo con la Clasificación Internacional de Patentes (IPC) o tanto la clasificación nacional como la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)
U.S.: 514/221, 222.8, 230.5, 252.17, 266.22; 540/500; 544/11, 71, 231, 284, 285, 286

Documentación buscada diferente de la documentación mínima, al grado que estos documentos se incluyen en los campos buscados.

Base de datos, electrónica, consultada durante la búsqueda internacional (nombre de la base de datos, donde se puede practicar, términos de búsqueda usados).
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No
X	WO 98/11128 A1 (DR. KARL THOMAE G.M.B.H.) 19 Marzo 1998, ver ejemplo No. 576, 580, 587 rtc.	1-6

[X] Documentos adicionales se listan en la continuación del cuadro C.

[X] Los miembros de la familia de patentes se listan en el anexo

* Categoría especial de los documentos citados:

"A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular

"E" Documento anterior, pero publicado en o después de la fecha de presentación internacional

"L" Documento que puede crear dudas de la reivindicación(es) de prioridad o que se cita para establecer la fecha de publicación de otra situación u otra razón especial (como se especifique)

"O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada

"T" documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se cita para entender el principio o teoría que trata la invención

"X" documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo

"Y" documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se combina con uno o más de estos documentos, estas combinaciones son obvias para una persona experta en la técnica

"&" documento miembro de la familia de patentes

Fecha de la actual terminación de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
24 Agosto 2004 (24.08.2004)	30 Agosto 2004

Nombre y dirección de envío ISA	Funcionario autorizado
Mail Stop PCT, TAJ: ISA/US Comisionado para Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax. No. (703) 305-3230	(rúbrica) Brenda Coleman Telefono No. 571-272-1600

Forma PCT/ISA/210 (hoja 2) (Julio 1992)

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, 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.

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 Preliminary 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 (Administrative Instructions, 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.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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Search result: 1 of 1

(WO/2005/065779) CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS

Biblio. Data | Description | Claims | National Phase | Notices | Documents

Latest bibliographic data on file with the International Bureau

Publication Number: WO/2005/065779 **International Application No.:** PCT/US2003/038799
Publication Date: 21.07.2005 **International Filing Date:** 05.12.2003

Int. Class.[7]: A61K 31/495, A61K 31/50, A61K 31/52, A61K 31/535, A61K 31/54, A61K 31/55, A61P 25/06, C07D 239/00, C07D 243/10, C07D 265/00, C07D 285/00

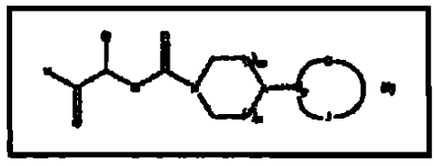
Applicants: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US) *(All Except US)*.
DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US) *(US Only)*.
CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US) *(US Only)*.
CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US) *(US Only)*.
DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US) *(US Only)*.
HAN, Xiaojun [CN/US]; 65 Ridgecrest Drive, Cheshire, CT 06410 (US) *(US Only)*.
JIANG, Xiang, Jun, J. [US/US]; 760 Mix Ave., #2L, Hamden, CT 06514 (US) *(US Only)*.
MACOR, John, E. [US/US]; 644 Mosse Hill Road, Guilford, CT 06437 (US) *(US Only)*.
TORA, George [KE/US]; 30 N. Meadow Lane, Meriden, CT 06450 (US) *(US Only)*.
→ LUO, Guanglin [CN/US]; 135 Devonshire Lane, Madison, CT 06443 (US) *(US Only)*.

Inventors: DEGNAN, Andrew, P. [US/US]; 123 York Street, Apt. 22-P, New Haven, CT 06511 (US).
CHEN, Ling [CN/US]; 193 McCormick Lane, Middletown, CT 06457 (US).
CIVIELLO, Rita [US/US]; 90 Cow Hill Road, Killingworth, CT 06419 (US).
DUBOWCHIK, Gene, M. [US/US]; 65 Spring Street, Middlefield, CT 06455 (US).
HAN, Xiaojun [CN/US]; 65 Ridgecrest Drive, Cheshire, CT 06410 (US).
JIANG, Xiang, Jun, J. [US/US]; 760 Mix Ave., #2L, Hamden, CT 06514 (US).
MACOR, John, E. [US/US]; 644 Mosse Hill Road, Guilford, CT 06437 (US).
TORA, George [KE/US]; 30 N. Meadow Lane, Meriden, CT 06450 (US).
→ LUO, Guanglin [CN/US]; 135 Devonshire Lane, Madison, CT 06443 (US).

Agent: MAKUJINA, Shah; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

Title: CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS

Abstract: The present invention relates to compounds of Formula (I) as antagonists of calcitonin gene-related peptide receptors ('CGRP-receptor'), pharmaceutical compositions comprising them, methods for identifying them, methods of treatment using them and their use in therapy for treatment of neurogenic vasodilation, neurogenic inflammation, migraine and other headaches, thermal injury, circulatory shock, flushing associated with menopause, airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and other conditions the treatment of which can be effected by the antagonism of CGRP-receptors.



Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
African Regional Intellectual Property Org. (ARIPO) (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW)
Eurasian Patent Organization (EAPO) (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM)
European Patent Office (EPO) (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)
African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML

African Intellectual Property Organization (OAPI) (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publication Language: English (EN)

Filing Language: English (EN)

26 934

Docket No. 10135-PCT

PATENT COOPERATION TREATY

International Application No.: PCT/US2003/038799
International Filing Date: 05 December 2003
International Publication No.: WO 2005/065779
International Publication Date: 21 July 2005
Priority Date: 05 December 2003
Applicant: Bristol-Myers Squibb Company, *et al.*

For: CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS

Via Facsimile: (41-22) 910 0610
and confirmation via Airmail

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

92 BIS CHANGE

Dear Sir:

Please amend the records in the above international application to reflect the addition of the following applicant/inventor: LUO, Guanglin, residing at 135 Devonshire Lane, Madison, Connecticut 06443 USA. Mr. Luo is a citizen of the People's Republic of China.

We enclose a copy of the Powers of Attorney form executed by the applicant, Bristol-Myers Squibb Company and the applicant/inventors, DEGNAN, Andrew P., CHEN, Ling, CIVIELLO, Rita, DUBOWCHIK, Gene M., HAN, Xiaojun, JIANG, Xiang Jun J., MACOR, John E. and TORA, George.

Docket No. 10135-PCT

Please note that the 30-month priority date is 05 June 2006. Accordingly, we would appreciate it if the change was recorded before that date. Please issue form PCT/IB/306 and forward it to us as soon as possible.

Respectfully submitted,

Date: 9/1/2005

Shah R. Makwana
Agent for Applicants
Reg. No. 41,174
Tel: (203) 677-7268

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000 USA

AAA:nst
Enclosures

964 936

PCT POWER OF ATTORNEY 10135PCT

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)

1	The undersigned applicant(s)	DEGNAN, Andrew, P.; CHEN, Ling; CIVIELLO, Rita; DUBOWCHIK, Gene, M.; HAN, Xiaojun; JIANG, Xiang, Jun, J.; MACOR, John, E.; TORA, George
1-1-1	hereby appoints (appoint) the following person	MARUJINA, Shah; RYAN, Richard; BABAJKO, Suzanne; BAXAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; VANATTEN, Mary, K.; VOLLES, Warren, K.; LAMERDIN, John; KORSEN, Elliott; EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS
1-4-2	Applicant's or agent's file reference	10135PCT
1-4-3	International application number (if already available)	PCT/US03/38799
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-2	Signature of applicant	3/3/2004
2-2-1	Name	DEGNAN, Andrew, P.

9 of 937

PCT POWER OF ATTORNEY

10135PCT

2-3	Signature of applicant	
2-3-1	Name	CHEN, Ling 03/04/2004
2-4	Signature of applicant	
2-4-1	Name	CIVIELLO, Rita March 01, 2004
2-5	Signature of applicant	
2-5-1	Name	DUBOWCHIK, Gene, M. 3/3/04
2-6	Signature of applicant	
2-6-1	Name	HAN, Xiaojun 3/3/2004
2-7	Signature of applicant	
2-7-1	Name	JIANG, Xiang, Jun, J. 03-01-04
2-8	Signature of applicant	
2-8-1	Name	MACOR, John, E. 3/4/04
2-9	Signature of applicant	
2-9-1	Name	TORA, George 03/03/04
3	Date	

965 938

PCT POWER OF ATTORNEY

10135PCT

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)

1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	MAKUJIMA, Shah; RYAN, Richard; BABAJKO, Suzanne; BAYAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephan, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; HERMENAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; VANATTEN, Mary, K.; VOLLES, Warren, K.; LAMERDIN, John; KORSEN, Elliott; EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS
1-4-2	Applicant's or agent's file reference	10135PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-1	Signature of applicant	Richard P. Ryan
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Richard P. Ryan
2-1-3	Capacity	Sr. Patent Counsel
3	Date	05 December 2003 (05.12.2003)

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko
Stephen B. Davis
Blair Q. Ferguson
John M. Kilcoyne
Christopher Klein
David Morse
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 22nd day of May 2002.

John L. McGoldrick
Executive Vice President
and General Counsel

Secretary

~~268~~ 940

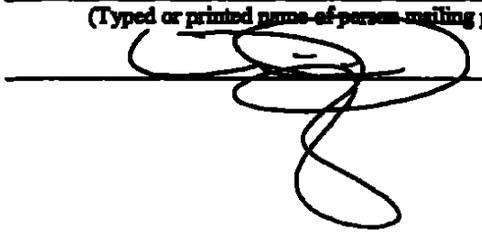
New PCT Application
Docket No.: 10135PCT
Priority Applications: None
Documents enclosed: Application, Fee Calculation Sheet, Power of Attorney for Bristol-Myers Squibb Company, PCT Easy Request, Diskette with Request and Abstract, Post Card Receipt.

Express mail mailing label number EV404516759US

Date of Deposit 12/5/03

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Mail stop PCT Application, P.O. Box 1450, Alexandria, VA 22313-1450.

Shah R. Malvijna
(Typed or printed name of person mailing paper or fee)



PCT REQUEST

10135PCT

Original (for SUBMISSION) - printed on 05.12.2003 07:58:37 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	10135PCT
I	Title of invention	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	DEGNAN, Andrew, P.
III-1-5	Address:	123 York Street, Apt. 22-P New Haven, CT 06511 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	CHEN, Ling
III-3-5	Address:	193 McCormick Lane Middletown, CT 06457 United States of America
III-3-6	State of nationality	CN
III-3-7	State of residence	US
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	CIVIELLO, Rita
III-3-5	Address:	90 Cow Hill Road Killingworth, CT 06419 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	DUBOWCHIK, Gene, M.
III-4-5	Address:	65 Spring Street Middlefield, CT 06455 United States of America
III-4-6	State of nationality	US
III-4-7	State of residence	US
III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	HAN, Xiaojun
III-5-5	Address:	65 Ridgecrest Drive Cheshire, CT 06410 United States of America
III-5-6	State of nationality	CN
III-5-7	State of residence	US
III-6	Applicant and/or Inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	JIANG, Xiang, Jun, J.
III-6-5	Address:	760 Mix Ave., #2L Hamden, CT 06514 United States of America
III-6-6	State of nationality	US
III-6-7	State of residence	US

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III-7	Applicant and/or inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	MACOR, John, E.
III-7-5	Address:	544 Mosse Hill Road Guilford, CT 06437 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
III-8	Applicant and/or inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	TORA, George
III-8-5	Address:	30 N. Meadow Lane Meriden, CT 06450 United States of America
III-8-6	State of nationality	HU
III-8-7	State of residence	US
IV-1	Agent or common representative; or address for correspondence	
	The person identified below is hereby/have been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	MAKUJINA, Shah
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	203-677-7268
IV-1-4	Facsimile No.	203-677-6900
IV-1-5	e-mail	shah.makujina@bms.com
IV-1-6	Agent's registration No.	41,174

IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	RYAN, Richard(30,491); BABAJKO, Suzanne(32,880); BAXAM, Deanna(45,266); BELFIELD, Jing(45,914); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen, C.(46,652); DAVIS, Stephen(26,693); DUNCAN, Laurelee(44,096); GIBBONS, Maureen(44,121); GOLIAN, Paul, D.(42,591); HERMENAU, Ronald(34,620); KLEIN, Christopher(34,363); LANGE, Keith(44,201); O'BRIEN, Maureen(42,043); PATEL, Rena(41,412); PEIST, Kenneth(45,006); PROVOOST, Jonathan(44,292); RODNEY, Burton(22,076); SHER, Andrey(39,024); ALGIERI, Aldo(31,697); DUBOFF, Samuel(25,969); VAMATTEN, Mary, K.(39,408); VOLLES, Warren, K.(33,810); LANDRUM, John(44,858); KORSEN, Elliott(32,705); EPPERSON, James(52,867)
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

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V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW	
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-8 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-8	Exclusion(s) from precautionary designations	NONE	
VI	Priority claim	NONE	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	-
IX-2	Description	357	-
IX-3	Claims	26	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	390	

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	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	MAKDJIDA, Shah	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

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0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional N°	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y Solicitud internacional PCT	

0-4	Forma – PCT/RO/101 petitoria	
0-4-1	Preparado usando	PCT-EASY Versión 2.92 (actualizada 01.11.2003)
0-5	Petición El abajo firmante pide que la presente solicitud sea tramitada de conformidad con el Tratado de Cooperación en materia de Patentes.	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo de solicitantes o agentes	10135PCR
I	TITULO DE LA INVENCION	ANTAGONISTA DEL RECEPTOR DE PEPTIDO RELACIONADO CON EL GEN DE CALCITONINA
II	Solicitante	
II-1	Esta persona es:	Solicitante únicamente
II-2	Solicitante para	Todos los estados designados excepto US
II-4	Nombre	BRISTOL-MYERS SQUIBB COMPANY
II-5	Dirección:	P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 Estados Unidos de América
II-6	Estado de Nacionalidad	US
II-7	Estado de Residencia	US
II-8	Teléfono No.	609-252-4000
II-9	Facsímile No.	609-252-4526
III-1	Solicitante y/o inventor	
III-1-1	Esta persona es:	Solicitante e inventor
III-1-2	Solicitante para	US solamente
III-1-4	Nombre (ULTIMO, Primero)	DEGNAN, Andrew, P.
III-1-5	Dirección	123 York Street, Apt. 22-P New Haven, CT 06511 Estados Unidos de América
III-1-6	Estado de Nacionalidad	US
III-1-7	Estado de Residencia	US
III-2	Solicitante y/o inventor	

III-2-1	Esta persona es:	Solicitante e inventor
III-2-2	Solicitante para	US solamente
III-2-4	Nombre (ULTIMO, Primero)	Chen, Ling
III-2-5	Dirección	193 McCormik Lane Middletowon, CT 06457. Estados Unidos de América
III-2-6	Estado de Nacionalidad	CN
III-2-7	Estado de Residencia	US
III-3	Solicitante y/o inventor	
III-3-1	Esta persona es:	Solicitante e inventor
III-3-2	Solicitante para	US solamente
III-3-4	Nombre (ULTIMO, Primero)	CIVIELLO, Rita
III-3-5	Dirección	90 Cow Hill Road Killingworth, CT 06419 Estados Unidos de América
III-3-6	Estado de Nacionalidad	US
III-3-7	Estado de Residencia	US
III-4	Solicitante y/o inventor	
III-4-1	Esta persona es:	Solicitante e inventor
III-4-2	Solicitante para	US solamente
III-4-4	Nombre (ULTIMO, Primero)	DUBOWCHIK, Gene, M.
III-4-5	Dirección	65 Spring Street Middlefield, CT 06455 Estados Unidos de América
III-4-6	Estado de Nacionalidad	US
III-4-7	Estado de Residencia	US
III-5	Solicitante y/o inventor	
III-5-1	Esta persona es:	Solicitante e inventor
III-5-2	Solicitante para	US solamente
III-5-4	Nombre (ULTIMO, Primero)	HAN, Xiaojun
III-5-5	Dirección	65 Ridgecrest Drive Cheshire. CT 06410 Estados Unidos de América
III-5-6	Estado de Nacionalidad	CN
III-5-7	Estado de Residencia	US
III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	Solicitante y/o inventor
III-6-2	Solicitante para	US solamente
III-6-4	Nombre (ULTIMO, Primero)	JIANG, Xiang, Jun, J.
III-6-5	Dirección	760 Mix Ave., #2L Hamden, CT 06514 Estados Unidos de América
III-6-6	Estado de Nacionalidad	US
III-6-7	Estado de Residencia	US
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	Solicitante y/o inventor
III-7-2	Solicitante para	US solamente
III-7-4	Nombre (ULTIMO, Primero)	MACOR, John, E.

III-7-5	Dirección	644 Moss Hill Road Guilford, CT 06437 Estados Unidos de América
III-7-6	Estado de Nacionalidad	US
III-7-7	Estado de Residencia	US
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	Solicitante y/o inventor
III-8-2	Solicitante para	US solamente
III-8-4	Nombre (ULTIMO, Primero)	TORA, George
III-8-5	Dirección	30 N. Meadow Lane Meriden, CT 06450 Estados Unidos de América
III-8-6	Estado de Nacionalidad	KE
III-8-7	Estado de Residencia	US
IV-1	Agente o representante común; o dirección para correspondencia La persona abajo identificada se designa/ha sido designada para actuar en nombre del/ de los solicitante(s) ante las administraciones internacionales competentes como:	Agente
IV-1-1	Nombre (ULTIMO, Primero)	MAKUJINA, Shah
IV-1-2	Dirección	Bristol-Myers Squibb Company P.O. Box 4000 Princenton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	203-677-7268 203-677-6900
IV-1-4	Fax No.	(612) 339-3061
IV-1-5	e-mail	shah.makujina@bms.com
IV-1-6	Numero de registro del agente	41,174
IV-2	Agentes adicionales	Agentes adicionales con la misma dirección como el primer agente nombrado
IV-2-1	Nombre (s)	RYAN, Tichard(30,491); BARBAJKO, Suzanne (32,880); BAXAM, Deanna (45,266); BELFIELD, Jing (45,914); BUCHHOLS, Briana (39,123); D'AMICO, Stephen, C. (46,652); DAVIS, Stephen (26,693); DUNCAN, Laurelee (44,096); GIBBONS, Maureen (44,121); GOLIAN, Paul, D. (42,591); HERMENAU, Ronald (34,620); KLEIN, Christopher (34,363); LANGE, Keith (44,201); O'BRIEN, Maureen (42,043); PATEL, Rena

		(41,412); PEIST, Kenneth (45,006); PROVOOST, Jonathan (44,292); RODNEY, Burton (22,076), CHER, Audrey (39,024); ALGIERI, Aldo(31,697); DUBOFF, Samuel (25,969); VANATTEN, Mary, K. (39,408); VOLLES, WARREN, k. (33,810); LAMERDIN, John (44,858); KORSEN, Elliott (32,705); EPPERSON, James (52,867)
V	Designación de estados	
V-1	Patente Regional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AP: BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW y cualquier otro estado que es un estado contratante del protocolo de Harare y del PCT. EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro estado que es un estado contratante de la convención de patentes eurasiáticos y del PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR y cualquier otro estado que son un estado contratante de la convención de patentes Europea y del PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG y cualquier otro estado que son estados miembros de OAPI y un estado contratante del estado del PCT
V-2	Patente Nacional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
V-5	Declaración de Designación Precautoria Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el	

	solicitante también hace bajo la Regla 4.9(b) todas las designaciones que puedan permitirse bajo el PCT excepto cualquier designación de los Estados indicados bajo el punto V-6 siguiente. El solicitante declara que aquellas designaciones adicionales están sujetas a la confirmación y que cualquier designación que no se confirme antes de la expiración de 15 meses a partir de la fecha de prioridad serán apreciadas como retiradas por el solicitante en la expiración de este tiempo límite		
V-6	Exclusión(s) para designaciones preventivas	NINGUNO	
VI	Reivindicación de Prioridad	NINGUNA	
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (ISA/US)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para la identidad del inventor	-	
VIII-2	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para solicitar y garantizar una patente	-	
VIII-3	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud previa	-	
VIII-4	Declaración de los inventores (sólo para los propósitos de designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones o excepciones no perjudiciales para carecer de novedad	-	
IX	Lista de revisión	Número de hojas	Archivos electrónicos anexos
IX -1	Petitorio	6	✔
IX -2	Descripción	357	-
IX-3	Reivindicaciones	26	-
IX -4	Resumen	1	EZABST00.TXT
IX -5	Dibujos	0	-
IX-7	Total	390	
	Puntos acompañantes	Papel de documento(s)	Archivo(s) electrónico anexo

		anexo	
IX-8	Hoja de calculo de tasa	✔	-
IX-9	Original del poder separado del apoderado	✔	✔
IX-17	Disco PCT-EASY	-	Disco
IX-18	Otro (especificar):	Certificación	-
IX-19	Se sugiere la figura de los dibujos para acompañar el resumen en el momento de su publicación.		
IX-20	Idioma de presentación de la solicitud internacional de patente	INGLES	
X-1	Firma del solicitante o del mandatario	Rúbrica	
X-1-1	Nombre (ULTIMO, Primero)	MAKUJINA, Shah	

PARA LA OFICINA RECEPTORA ÚNICAMENTE

10-1	Fecha efectiva de recepción de la pretendida solicitud internacional	
10-2 10-2-1 10-2-2	Dibujos Recibidos No recibidos	
10-3	Fecha efectiva de recepción, rectificada de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completa la pretendida solicitud internacional	
10-4	Fecha de recepción, dentro del plazo de las correcciones solicitadas según el Articulo 11(2) del PCT	
10-5	Autoridad de búsqueda internacional	ISA/US
10-6	Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda	

PARA USO UNICAMENTE DE LA OFICINA INTERNACIONAL

11-1	Fecha de recepción del ejemplar Original por la Oficina Internacional	

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PCT (ANNEX - FEE CALCULATION SHEET) 10135PCT

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(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)		
0-9	Applicant's or agent's file reference	10135PCT		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇨	240	
12-2-1	Search fee S	⇨	700	
12-2-2	International search to be carried out by	US		
12-3	International fee Basic fee (first 30 sheets) b1	476		
12-4	Remaining sheets	360		
12-5	Additional amount (X)	12		
12-6	Total additional amount b2	4,320		
12-7	b1 + b2 = B	4,796		
12-8	Designation fees Number of designations contained in international application	99		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (X)	104		
12-11	Total designation fees D	520		
12-12	PCT-EASY fee reduction R	-148		
12-13	Total international fee (B+D-R) I	⇨	5,168	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇨	6,108	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.	✓		
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓		
12-20-3	Authorization to charge the fee for priority document.	✓		
12-21	Deposit account No.	19-3880		
12-22	Date	05 December 2003 (05.12.2003)		

PCT (ANNEX - FEE CALCULATION SHEET) 10135PCT

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12-23	Name and signature	MAKWANA, Shah

VALIDATION LOG AND REMARKS

13-2-4	Validation messages Priority	Green? No priority of an earlier application has been claimed. Please verify
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

PCT POWER OF ATTORNEY

10135PCT

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)

1	The undersigned applicant(s)	DEGHAN, Andrew, P.; CHEN, Ling; CIVIELLO, Rita; DUBOWCHIK, Gene, M.; HAN, Xiaojun; JIANG, Xiang, Jun, J.; MACOR, John, E.; TORA, George
1-1-1	hereby appoints (appoint) the following person	MAKUJINA, Shah; RYAN, Richard; BABAJKO, Suzanne; BAYAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; HEIMENDAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Audrey; ALGIERI, Aldo; DUBOFF, Samuel; VANATTEN, Mary, K.; VOLLES, Warren, K.; LAMERDIN, John; KORSEN, Elliott; EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS.
1-4-2	Applicant's or agent's file reference	10135PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-2	Signature of applicant	
2-3-1	Name	DEGHAN, Andrew, P.

PCT POWER OF ATTORNEY

10135PCT

2-3	Signature of applicant	
2-3-1	Name	CHEN, Ling
2-4	Signature of applicant	
2-4-1	Name	CIVIELLO, Rita
2-5	Signature of applicant	
2-5-1	Name	DUBOWCHIK, Gene, M.
2-6	Signature of applicant	
2-6-1	Name	HAN, Xiaojun
2-7	Signature of applicant	
2-7-1	Name	JIANG, Xiang, Jun, J.
2-8	Signature of applicant	
2-8-1	Name	MACOR, John, E.
2-9	Signature of applicant	
2-9-1	Name	TORA, George
3	Date	05 December 2003 (05.12.2003)

9 of 97

PCT POWER OF ATTORNEY 10135PCT

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 90.4)	
0-1-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)

1	The undersigned applicant(s)	BRISTOL-MYERS SQUIBB COMPANY
1-1-1	hereby appoints (appoint) the following person	MAKUJINA, Shah; RYAN, Richard; BARAJKO, Suzanne; BAKAM, Deanna; BELFIELD, Jing; BUCHHOLZ, Briana; D'AMICO, Stephen, C.; DAVIS, Stephen; DUNCAN, Laurelee; GIBBONS, Maureen; GOLIAN, Paul, D.; HERMSMAU, Ronald; KLEIN, Christopher; LANGE, Keith; O'BRIEN, Maureen; PATEL, Rena; PEIST, Kenneth; PROVOOST, Jonathan; RODNEY, Burton; SHER, Andrey; ALGIERI, Aldo; DUBOFF, Samuel; VANATTEN, Mary, K.; VOLLES, Warren, K.; LAMERDIN, John; KORSEN, Elliott; EPPERSON, James Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of the invention	CALCITONIN GENE RELATED PEPTIDE RECEPTOR ANTAGONISTS
1-4-2	Applicant's or agent's file reference	10135PCT
1-4-3	International application number (if already available)	
1-4-4	filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned.	

2-1	Signature of applicant	Richard P. Ryan
2-1-1	Name	BRISTOL-MYERS SQUIBB COMPANY
2-1-2	Name of signatory	Richard P. Ryan
2-1-3	Capacity	Sr. Patent Counsel
3	Date	05 December 2003 (05.12.2003)

CERTIFICATION

The undersigned, being the Executive Vice President and General Counsel of Bristol-Myers Squibb Company, hereby designates:

Suzanne Babajko
Stephen B. Davis
Blair Q. Ferguson
John M. Kilcoyne
Christopher Klein
David Morse
Richard Ryan

(a) to present to the Patent, Trademark, Copyright and similar Government Offices of all countries or to any competent authority, all original, divisional, continuation and reissue applications, petitions and request in the name of Bristol-Myers Squibb Company and its subsidiary companies, for letters patent for inventions, utility models, industrial models and designs and improvements or additions thereof, trademarks and copyrights; (b) to initial and prosecute oppositions and appeals; (c) to appear before all officers duly authorized, all Ministers, Bureaus, Clerk's Offices and Commissions or Commissioners that may be necessary; (d) to sign and approve on behalf of this corporation all documents and powers of attorney which judgment of the authorized individuals may be necessary or desirable to carry out the powers hereby conferred; (e) to request all proceedings; (f) to pay over or withdraw all taxes, obtain receipts therefor and give discharge; (g) to withdraw applications and all documents relating thereto; (h) to commence proceedings against infringers and assure the defense in infringement actions; and (i) generally to do all that in the judgment of the authorized individual may be necessary to secure granting of the privileges above-mentioned.

IN WITNESS WHEREOF, I have placed my hand and caused the seal of the Company to be affixed hereto on this 22nd day of May 2002.

John L. McGoldrick
Executive Vice President
and General Counsel

Secretary

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MAURA O KNOBL

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MAURA O KNOBL, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

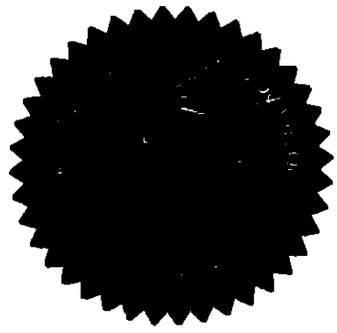
6. THE 13TH DAY OF JANUARY 2006

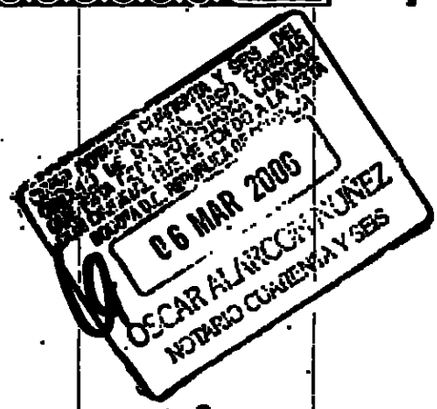
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A248886

9. SEAL/STAMP:

10. SIGNATURE





488 960

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO**, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO**, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) BRISTOL-MYERS SQUIBB COMPANY

domiciled in Princeton, New Jersey, USA

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

this 11th day January 2006

Signature

Name Suzanne E. Babajko

Title Senior Patent Counsel

06 MAR 2006
OSCAR A. AFCON NUÑEZ
NOTARIO CUARENTA Y SEIS

9+4 961

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

CERTIFICADO NOTARIAL
PERSONA NATURAL

Hoy de de , compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 11 day of January of 2006 personally appeared before me SUZANNE E. BABAJKO

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
SENIOR PATENT COUNSEL

of BRISTOL-MYERS SQUIBB COMPANY

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of
under date of

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

NOTARIAL CERTIFICATE
NATURAL PERSON

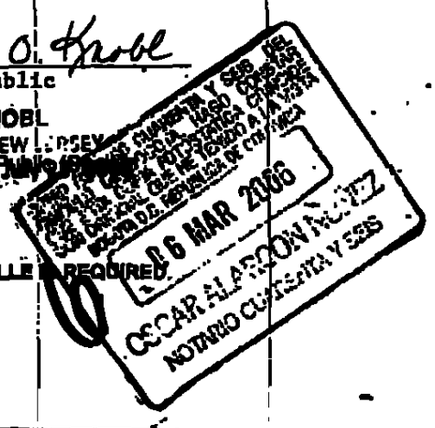
On this 11th day of January of 2006
personally appeared before me
Suzanne E. Babajko
who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Maura O. Knobl
Notary Public

MAURA O. KNOBL
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires July 6, 2009

Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED.



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962

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en **Princeton, New Jersey, Estados Unidos de América.**

APOSTILLA

(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PUBLICO HA SIDO FIRMADO POR:
MAURA O KNOBL

3. ACTUANDO EN CAPACIDAD DE:
NOTARIO PUBLICO DE NEW JERSEY

4. LLEVA EL SELLO/TIMBRE DE:
MAURA O KNOBL, NOTARIO

CERTIFICADO

5. EN TRENTON, NEW JERSEY

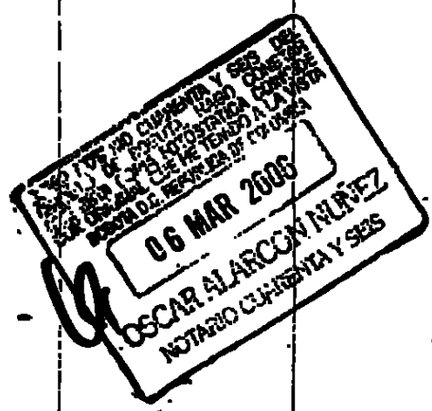
6. EL 13 DE ENERO DE 2006

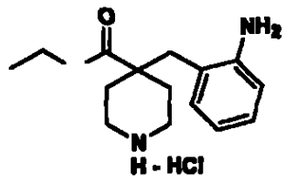
7. POR: John E. McCormac, CPA, TESORERO DE NEW JERSEY

8. NO. A248886

9. SELLO/TIMBRE: 10. FIRMA

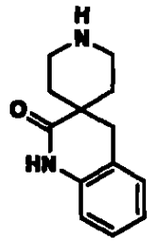
(Firma)





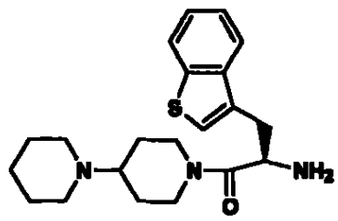
To a solution of 4-(2-amino-benzyl)-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (1.29 g, 4.102 mmol) in dichloromethane (15 mL) was added a 4.0M solution of hydrogen chloride in dioxane (5 mL). The resulting solution was stirred at room temperature overnight. The concentration of the solution under vacuum provided the title compound (1.23 g, 100%) as white solid, which was used in the next step without purification. Mass spec.: 263.40 $(MH)^+$.

3,4-Benzo-2,9-diazaspiro[5.5]undeca-1-one



A solution of 4-(2-amino-benzyl)-piperidine-4-carboxylic acid ethyl ester hydrochloride (1.23 g, 4.102 mmol) was dissolved in methanol and the resulting solution was stirred at room temperature overnight. The solution was diluted by half with water and passed through a short plug of the hydroxide form of AG® 1-X2 ion-exchange resin (100-200 mesh), eluting with 50% aqueous methanol. The evaporation of the collected fractions gave the desired product (0.89 g, 100%) as white solid. ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.23 (m, 2H), 7.05 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 3.46-3.41 (m, 2H), 3.34-3.30 (m, 2H), 2.14-2.09 (m, 2H), 1.73-1.67 (m, 4H). Mass spec.: 217.46 $(MH)^+$.

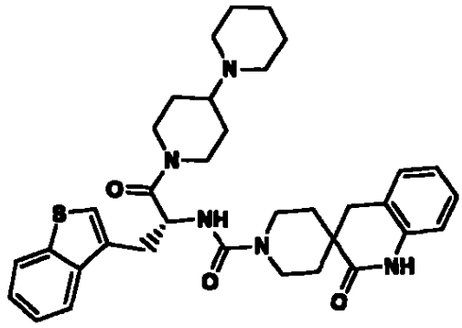
(R)-2-Amino-3-benzo[b]thiophen-3-yl-1-[1,4']bipiperidinyl-1'-yl-propan-1-one, dihydrochloride



To a well stirred solution of 3-benzo[b]thiophen-3-yl-(2R)-2-*tert*-butoxycarbonylamino-propionic acid (1.0 g, 3.1 mmol) in methylene chloride (30 mL) at room temp was added 4-piperidinopiperidine (573 mg, 3.4 mmol), triethylamine (1.3 mL, 9.3 mmol) followed by 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (1.02 g, 3.4 mmol). After 3 h, the reaction mixture was treated with aqueous sodium hydrogencarbonate (15 mL), brine (20 mL) and dried (sodium sulfate). The crude mixture was purified by flash chromatography using 5% methanol in methylene chloride to give (1R)-1-benzo[b]thiophen-3-ylmethyl-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl)-carbamic acid *tert*-butylester in 82% yield. (1R)-1-Benzo[b]thiophen-3-ylmethyl-2-[1,4']bipiperidinyl-1'-yl-2-oxo-ethyl)-carbamic acid *tert*-butylester (1.2 g, 2.54 mmol) in methylene chloride (5 mL) was added to a saturated solution of hydrogen chloride in dioxane (20 mL) and stirred for 2 h. The solvents were removed to give (2R)-2-amino-3-benzo[b]thiophen-3-yl-1-[1,4']bipiperidinyl-1'-yl-propan-1-one,dihydrochloride in 98% yield. ^{1}H-NMR (500 MHz, CD_3OD): δ 7.98 - 7.88 (m, 2 H), 7.55 - 7.40 (m, 3 H), 4.85 - 4.83 (m, 1 H), 3.66 - 2.68 (m, 9 H), 1.92 - 1.44 (m, 12 H). Mass spec.: 372 $(MH)^+$.

Example 61

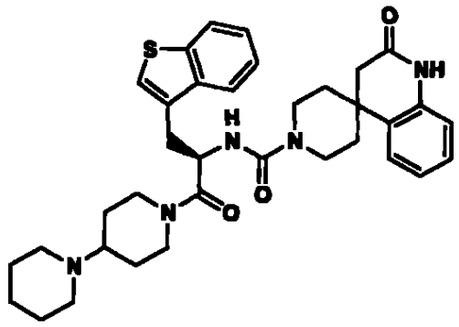
(R)-1-Oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide



To a solution of 2-amino-3-benzo[*b*]thiophen-3-yl-1-[1,4'] bipiperidinyl-1'-yl-propan-1-one (50.0 mg, 0.135 mmol) in 1,2-dichloroethane (1.5 mL) were added *N,N'*-disuccinimidyl carbonate (34.6 mg, 0.135 mmol) and diisopropylethyl amine (0.09 mL, 0.500 mmol). The resulting solution was stirred for 1 h, at which point 3,4-benzo-2,9-diazaspiro[5.5]undeca-1-one (30.4 mg, 0.140 mmol) was added. The reaction mixture was stirred at room temperature overnight and concentrated. The purification was achieved by way of reversed-phase preparative HPLC to give the desired product (75.5 mg, 77%) as brown oil. ^{1}H-NMR (CD_3OD, 500 MHz) δ 7.92-7.85 (m, 2H), 7.44-7.34 (m, 3H), 7.21-7.16 (m, 2H), 7.00 (t, *J* = 7.0 Hz, 1H), 6.86 (t, *J* = 8.5 Hz, 1H), 5.15-5.02 (m, 1H), 4.72-4.45 (m, 1H), 3.95-3.20 (m, 8H), 3.18-2.92 (m, 4H), 2.92-2.75 (m, 2H), 2.75-2.63 (m, 1H), 2.40-2.30 (m, 1H), 2.08-1.64 (m, 8H), 1.58-1.20 (m, 6H). Mass spec.: 614.37 $(MH)^+$.

Example 62

N-[(1R)-1-(Benzo[b]thien-3-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-3',4'-dihydro-2-oxospiro-[piperidine-4,4'(1H)-quinoline]-1-carboxamide

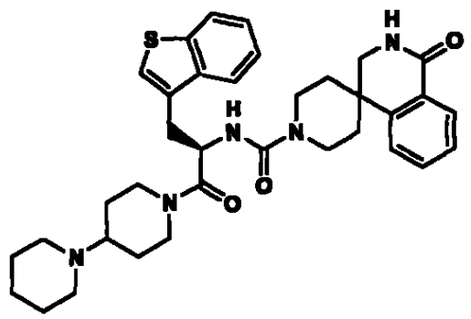


Prepared as described for (R)-1-oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide from 3',4'-dihydro-2-oxospiro-[piperidine-4,4'(1H)-quinoline (M.S. Chambers, et al., J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ -0.35 (1H, m), 0.79 (1H, m), 1.2-2.1 (12H, m), 2.22 (5H, m), 2.38 (2H, m), 2.74 (2H, ABq), 3.19 (3H, m), 3.33 (2H, m), 3.65 (1H, d), 3.80 (1H, m), 3.93 (1H, t), 4.49 (1H, d), 5.31 (1H, t), 5.96 (1H, t), 6.89 (1H, d), 7.05 (1H, t), 7.18 (1H, d), 7.26 (1H, m), 7.33 (1H, m), 7.40 (1H, m), 7.78 (1H, m), 7.96 (1H, Abq), 9.01 (1H, brs), 9.17 (1H, brs). Mass spec.: 614.36 $(MH)^+$.

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Example 63

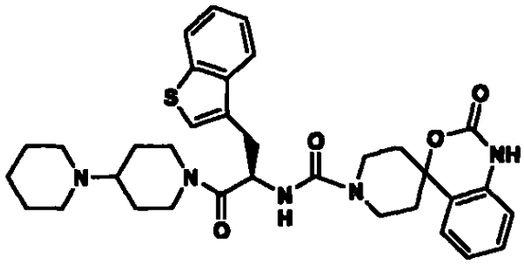
N-[(1R)-1-(Benzo[b]thien-3-ylmethyl)-2-[1,4-bipiperidin]-1-yl-2-oxoethyl]-2',3'-dihydro-1-oxospiro-[piperidine-4,4'(1H)-isoquinoline]-1-carboxamide



Prepared as described for (R)-1-oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide from 2',3'-dihydro-1-oxospiro-[piperidine-4,4'(1H)-isoquinoline (M.S. Chambers, et al., J. Med. Chem., 1992, 35, 2033-2039; WO-94/13696). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.01 (1H, m), 0.78 (1H, m), 1.1-2.0 (12H, m), 2.15-2.30 (5H, m), 2.74 (1H, t), 3.0-3.6 (9H), 3.89(2H, m), 4.46 (1H, d), 5.29 (1H, m), 5.62 (1H, d), 6.47 (1H, brs), 7.38 (5H, m), 7.51 (1H, m), 7.77 (1H, m), 7.85 (1H, m), 8.11 (1H, d). Mass spec.: 614.42 $(MH)^+$.

Example 64

N-[(1R)-1-(Benzo[b]thien-3-ylmethyl)-2-[1,4'-bipiperidin]-1'-yl-2-oxoethyl]-1,2-dihydro-2-oxospiro-[4H-3,1-benzoxazine-4,4'-piperidine]-1'-carboxamide

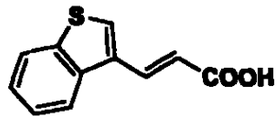


Prepared as described for (R)-1-oxo-3,4-benzo-2,9-diaza-spiro [5.5] undec-3-ene-9-carboxylic acid (1–benzo [*b*] thiophen-3-ylmethyl-2-[1,4'] bipiperidinyl-1'-yl-2–oxo-ethyl)-amide from 1,2-dihydro-2-oxospiro-[4H-3,1-benzoxazine-4,4'-

piperidine (prepared as described in Takai, et al.; Chem. Pharm. Bull. 1985, 33, 1129-1139) to give the title compound (76%). Mass spec.: 616 $(MH)^+$. R_f= 1.42.

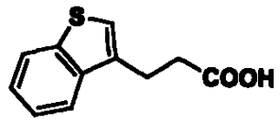
Succinate Intermediates and Examples

3-Benzo[b]thiophen-3-yl-acrylic acid



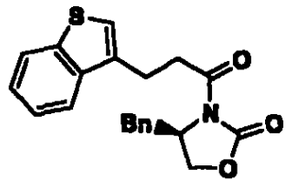
A suspension of 1-benzothiophene-3-carbaldehyde (4.9 g, 0.03 mol), malonic acid (6.6 g, 0.06 mol) and piperidine (1 mL) in 100 mL anhydrous pyridine was heated at 110°C overnight. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was taken up in 100 mL of water and 1 N hydrochloric acid was added to adjust the pH of this solution to ca. 3. The suspension was filtered and the yellow solid was collected, washed with water (3 x 50 mL) and concentrated *in vacuo* to give the indicated product with 95% purity (5.65g, 91%).

3-Benzo[b]thiophen-3-yl-propionic acid



A suspension of 3-benzo[b]thiophen-3-yl-acrylic acid: (5.6 g, 0.027 mol) and 10% Pd/C (600 mg) in 1:1 methanol/ethyl acetate (50 mL) was hydrogenated in a Parr apparatus at 50 psi overnight. The mixture was filtered and concentrated to give the crude product without further purification (ca.100% conversion). Mass spec.: 205$(MH)^-$.

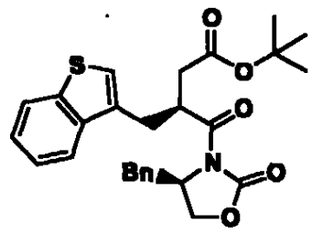
3-(3-Benzo[b]thiophen-3-yl-propionyl)-4(R)-benzyl-oxazolidin-2-one



946
960

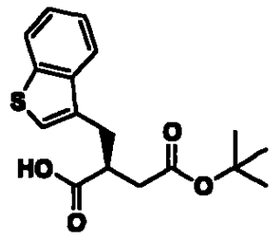
To a solution of 3-benzo[b]thiophen-3-yl-propionic acid (2.1g, 0.010 mol), triethylamine (4.12 g, 0.040 mol) in anhydrous tetrahydrofuran (100 mL) at 0°C was added pivaloyl chloride (1.38 mL, 0.011 mol). After stirring for 1.5 h at 0°C, lithium chloride (0.475 g, 0.011 mol) and (*R*)-4-benzyl-2-oxazolidinoe (1.988 g, 0.011 mol) were added. The reaction mixture was allowed to warm up to room temperature and stirred overnight. Then the mixture was washed with water (3 x 150 mL). The organic layer was separated, dried, and evaporated to give the crude product. The title product was obtained as a brown oil (90%) by flash chromatography on silica gel eluting with 100% methylene chloride . This compound was used immediately in the following procedure.

3(S)-Benzo[b]thiophen-3-ylmethyl-4-(4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxo butyric acid *tert*-butyl ester



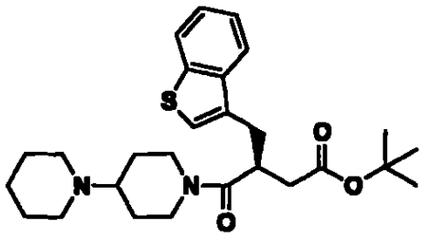
To a solution of 3-(3-benzo[b]thiophen-3-yl-propionyl)-4-benzyl-oxazolidin-2-one (3.35 g, 9.18 mmol) in 100 mL anhydrous tetrahydrofuran at –78°C was added lithium diisopropyl amide in tetrahydrofuran (6.1 mL, 11.01 mmol) and the reaction mixture was stirred for 30 min Following addition of *t*-butyl bromoacetate (1.62 mL, 11.01 mmol) at –78°C, the mixture was stirred overnight while it was allowed to warm to room temperature. The solvent was evaporated and the residue diluted with ethyl acetate. The organic layer was washed with water (3 x 100 mL), dried, filtered, and concentrated to give the crude product. The title product was obtained by filtration through a pad of silica, eluting with methylene chloride (49 %).

2(S)-Benzo[b]thiophen-3-ylmethyl-succinic acid, 4-*tert*-butyl ester



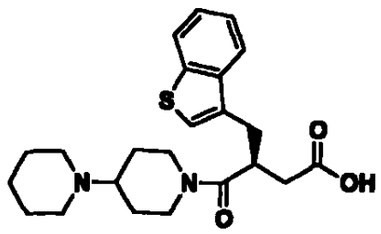
To a stirred solution of 3-benzo[b]thiophen-3-ylmethyl-4-(4-benzyl-2-oxo-oxazolidin-3-yl)-4-oxobutyric acid *tert*-butyl ester (2.15 g, 4.49 mmol) in tetrahydrofuran (50 mL) and water (30 mL) at 0°C was added 30 % aqueous hydrogen peroxide (1 mL) followed by lithium hydroxide (0.2155 g, 8.98 mmol). The reaction mixture was stirred overnight. Tetrahydrofuran was removed *in vacuo* and the resulting solution was acidified with 10% citric acid, and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with sodium bisulfite solution, dried and concentrated to give the title product.

3(S)-Benzo[b]thiophen-3-ylmethyl-4-[1,4']bipiperidinyl-1'-yl-4-oxo-butyric acid *tert*-butyl ester



A solution of 2-benzo[b]thiophen-3-ylmethyl-succinic acid 4-*tert*-butyl ester (1.8420 g, 5.76 mmol), piperidylpiperidine (1.2240 g, 7.28 mmol) and triethylamine (0.7353 g, 7.28 mmol) in 100 mL methylene chloride was treated with 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 1.8953 g, 6.34 mmol). The mixture was stirred overnight and then washed with water (3 x 40 mL). The organic layer was dried, filtered, and concentrated *in vacuo* to give the crude product. This was further purified by flash chromatography on silica gel, eluting with 0-10% 2 M ammonia in methanol/methylene chloride, to give the desired product. This product was carried on without further purification.

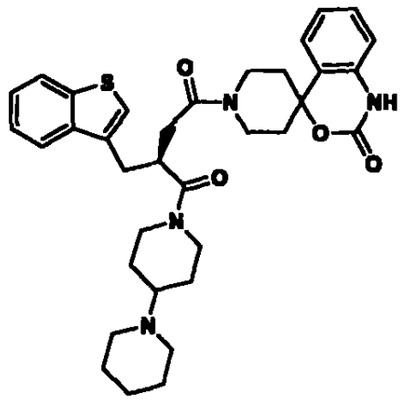
3(S)-Benzo[b]thiophen-3-ylmethyl-4-[1,4']bipiperidinyl-1'-yl-4-oxo-butyric acid



A solution of 3-benzo[b]thiophen-3-ylmethyl-4-[1,4']bipiperidinyl-1'-yl-4-oxo-butyric acid *tert*-butyl ester in 15 mL methylene chloride was treated with trifluoroacetic acid (3 mL) and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated to give the corresponding trifluoroacetate salt of the title product (99%).

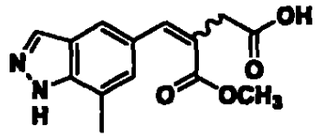
Example 65

1-[1,4']Bipiperidinyl-1'-yl-2-(3(S)-Benzo[b]thiophen-3-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



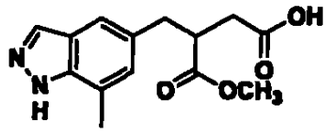
A solution of 3-benzo[b]thiophen-3-ylmethyl-4-[1,4']bipiperidinyl-1'-yl-4-oxo-butyric acid (25.0 mg, 0.060 mmol), 1,2-dihydro-2-oxospiro-4H-3,1-dihydro-benzoxazine-4'4-piperidine (15.7 mg, 0.072 mmol) and triethylamine (7.3 mg, 0.072 mmol) in 5 mL methylene chloride at room temperature was treated with 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 21.5 mg, 0.072 mmol). The solution was stirred overnight and then washed with water (3 x 5 mL). The organic layer was dried, concentrated, and the crude product was purified by flash chromatography on silica gel, eluting with 0-10% 2M ammonia in methanol/methylene chloride, to give the desired product in 60% yield. LC/MS: t_R=1.34 min, 615.45 $(MH)^+$.

2-(7-Methyl-1H-indazol-5-ylmethylene)-succinic acid 1-methyl ester



To a mixture of 7-methyl indazole aldehyde (0.2619 g , 1.64 mmol) and DBE-4 dibasic ester (dimethyl succinate) (0.32 mL, 2.45 mmol) in *t*-butanol (20 mL) was added potassium *t*-butoxide (0.4036 g, 3.60 mmol). The reaction mixture was heated at 50°C for 2h under nitrogen. After a further 16h at room temperature, the solvent was removed *in vacuo* and the residue was taken up in water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The aqueous layer was acidified with 1 N hydrochloric acid to pH 3 ~ 4 and extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate solution was dried and concentrated *in vacuo* to give the crude product as a yellow solid (99%, cis/trans isomer approximately 40:60). The crude mixture was carried to next step without further purification. Mass spec.: 275 $(MH)^+$.

(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-succinic acid 1-methyl ester

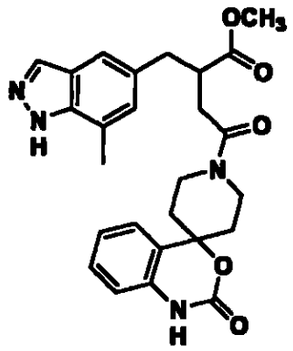


A suspension of 2-(7-methyl-1H-indazol-5-ylmethylene)-succinic acid 1-methyl ester (0.4440 g, 1.62 mmol) and 10% Pd/C (0.04 g) in ethyl acetate (15 mL) and methanol (5 mL) was hydrogenated in a Parr apparatus overnight at 50 psi. The reaction mixture was filtered through a pad of celite and the filtrate evaporated to give the desired product as a yellow solid (100%). Mass spec.: 277 $(MH)^+$.

Example 66

(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid methyl ester

1000 972

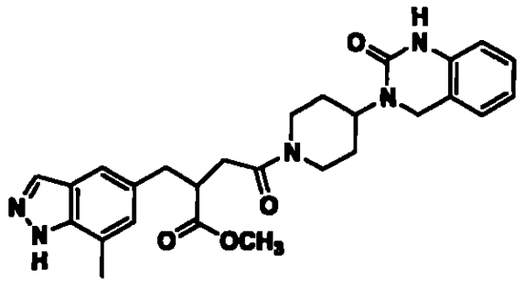


A solution of 2-(7-methyl-1H-indazol-5-ylmethyl)-succinic acid 1-methyl ester (0.2253 g, 0.82 mmol), 1,2-dihydro-2-oxospiro-4H-3,1-dihydro-benzoxazine-4'4-piperidine (0.1938 g, 0.89 mmol) and triethylamine (0.099 g, 0.98 mmol) in methylene chloride (15 mL) was treated with 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 0.2685 g, 0.90 mmol). The mixture was stirred overnight and then washed with water (3 x 5 mL). The organic layer was dried, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with 0-10% 2M ammonia in methanol/methylene chloride, to afford the desired product (53%). *LC/MS*: t_R=1.40 min, 477.28 $(MH)^+$.

Similarly prepared:

Example 67

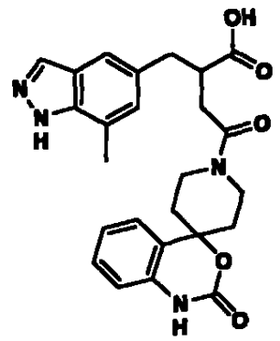
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid methyl ester



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.98(1H, m), 7,90 (1H, m), 7.35 - 6.89 (4H, m), 6.72 (1H, m), 4.71(1H, m), 4.57(1H, m), 4.27 (1H, s), 4.22 (1H, m), 3.85 (1H, m), 3.65 (3H, m), 3.30 (1H, m), 3.11(2H, m), 2.83 (2H, m), 2.81 - 2.54 (4H, m), 2.35 (1H, m), 1.7 3 - 1.67 (4H, m). Mass spec.: 490.32 $(MH)^+$.

1001 973

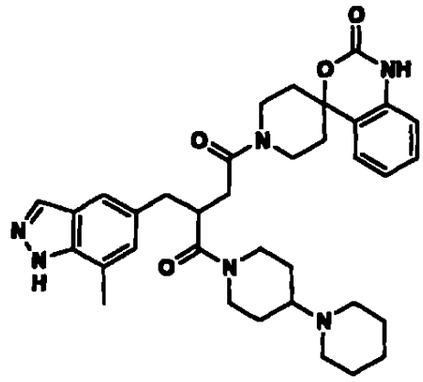
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid



A solution of 2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid methyl ester (0.1911 g, 0.40 mmol) and lithium hydroxide (19.3 mg, 0.80 mmol) in tetrahydrofuran (10 mL) and water (8 mL) was stirred overnight at room temperature. The reaction mixture was acidified with 1N hydrochloric acid to ca. pH 1 and concentrated to remove tetrahydrofuran *in vacuo* to afford a white solid precipitate which was collected by filtration. The solid was washed twice with small amounts of water and dried *in vacuo* overnight (100%). Mass spec.: 477 $(MH)^+$.

Example 68

(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



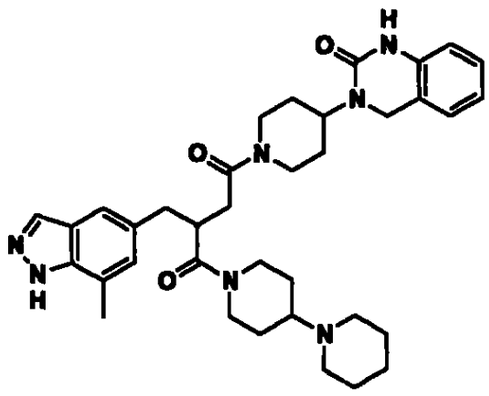
A solution of 2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyric acid (0.020 g, 0.04 mmol), piperidylpiperidine (0.0087 g, 0.05 mmol) and triethylamine (0.09 g, 0.08 mmol) in methylene chloride (5 mL) at room temperature was treated with 3-

(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 0.0155 g, 0.05 mmol). The mixture was stirred overnight and then washed with water (3 x 5 mL). The organic layer was dried and the solvents were removed *in vacuo*. The crude product was purified by preparative TLC on silica gel (10% 2 M ammonium hydroxide/methanol in methylene chloride) to give the desired product (36%). *LC/MS*: t_R=1.18 min, 613.47 $(MH)^+$.

Similarly prepared:

Example 69

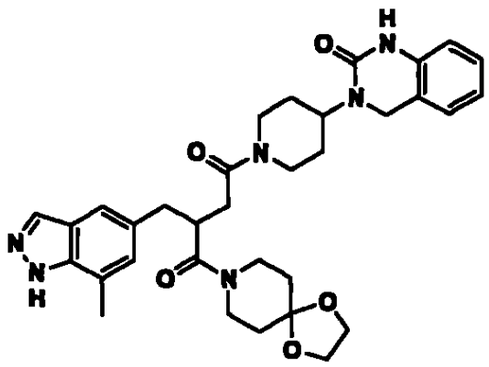
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, m), 7.62 (1H, m), 7.38 (1H, m), 7.14(1H, m), 7.04 - 6.90 (3H, m), 6.70 (2H, d, J=8.0 Hz), 4.70-4.58 (3H, m), 4.24 (2H, m), 4.00 (2H, m), 3.70 (1H, m), 3.18 - 2.72 (5H, m), 2.64 - 2.22 (8H, m), 2.18 - 0.82 (17H, m). Mass spec.: 626.34 $(MH)^+$.

Example 70

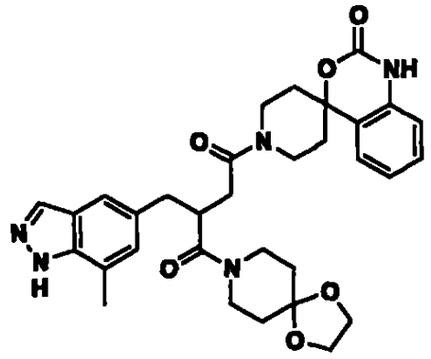
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(7-methyl-1H-indazol-5- ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, s), 7.75 (1H, m), 7.36 (1H, m), 7.14 (1H, m), 7.01 - 6.79 (3H, m), 6.70 (1H, m), 4.70 - 4.49 (2H, m), 4.23 (2H, m), 3.98 (1H, m), 3.87 (3H, m), 3.65 - 3.44 (4H, m), 3.26 (1H, m), 3.10 - 2.88 (3H, m), 2.75 (1H, m), 2.51 (3H, s), 2.35 (1H, m), 2.00 (1H, m), 1.70 - 1.00 (9H, m). Mass spec.: 601.38 $(MH)^+$.

Example 71

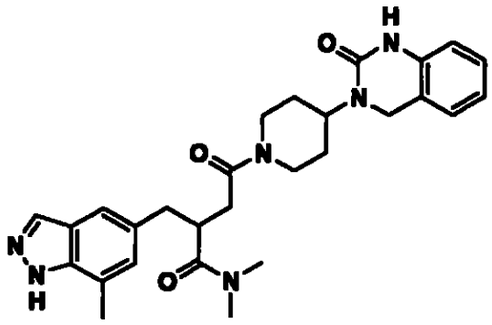
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(7-methyl-1H-indazol-5- ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.27 (1H, m), 8.00 (1H, s), 7.37 (1H, m), 7.23 (1H, m), 7.10 - 6.99 (3H, m), 6.87 (1H, m), 4.54 (1H, m), 3.97 - 3.50 (10H, m), 3.30 (1H, m), 3.16 - 2.76 (4H, m), 2.53 (3H, s), 2.35 (1H, m), 2.20 - 1.00 (9H, m). Mass spec.: 588.36 $(MH)^+$.

Example 72

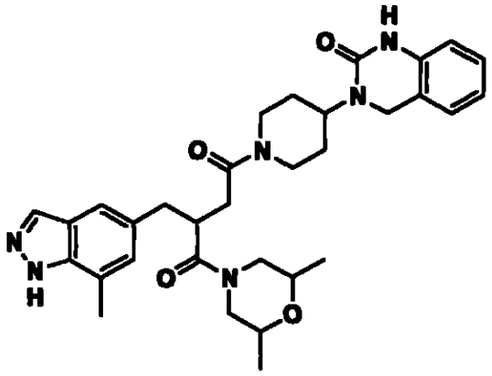
(±)-*N,N*-Dimethyl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyramide



LC/MS: t_R=1.36 min, 525.35 $(M+Na)^+$.

Example 73

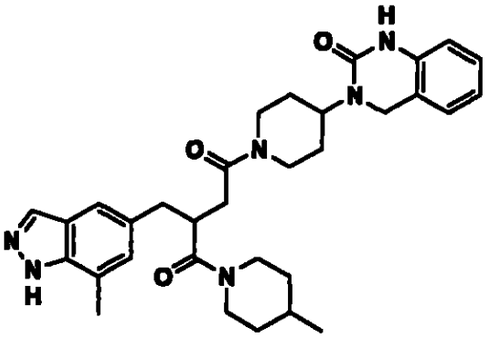
(±)-1-(2,6-Dimethyl-morpholin-4-yl)-2-(7-methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R=1.41 min, 573.39 $(MH)^+$.

Example 74

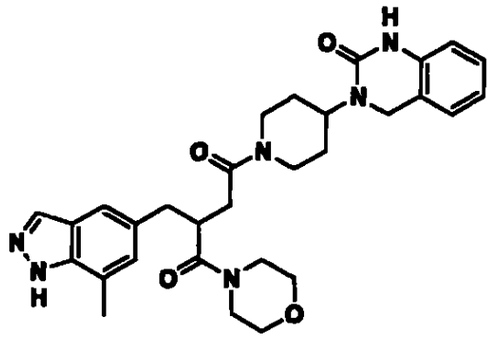
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-1-(4-methyl-piperidin-1-yl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, b), 7.60 - 6.73 (7H, m), 4.71 (1H, m), 4.54 (2H, m), 4.26 (2H, m), 4.05 - 3.89 (2H, m), 3.65 (1H, m), 3.09 - 2.81 (4H, m), 2.61 (3H, s), 2.41 (2H, m), 1.76 – 0.51(15H, m). Mass spec.: 557.38 $(MH)^+$.

Example 75

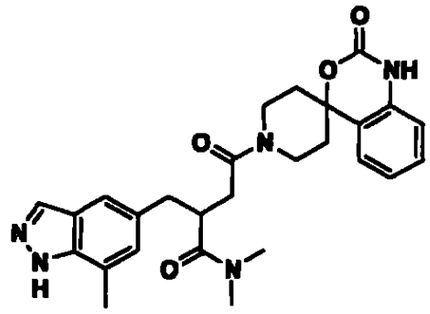
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-1-morpholin-4-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R=1.32 min, 545.42 $(MH)^+$.

Example 76

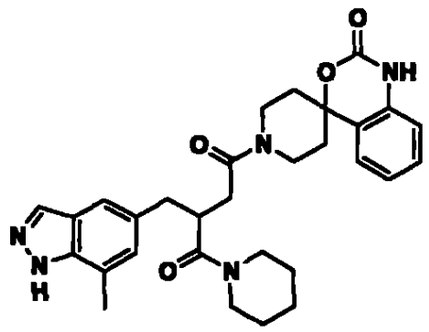
(±)-*N,N*-Dimethyl-2-(7-methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butyramide



LC/MS: t_R=1.27 min, 512.30 $(M+Na)^+$.

Example 77

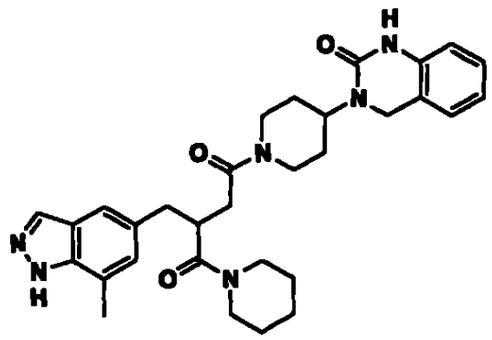
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-1-(piperidin-1-yl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.26 - 9.01 (1H, m), 8.09 (1H, s), 7.42 - 6.89 (7H, m), 4.56 (1H, m), 3.84 (1H, m), 3.65 (3H, m), 3.30 (2H, m), 3.05 (3H, m), 2.81 (1H, m), 2.60 (3H, s), 2.39 (1H, m), 2.09 (2H, m), 1.85 (1H, m), 1.43 - 0.79 (9H, m). Mass spec.: 530.34 $(MH)^+$.

Example 78

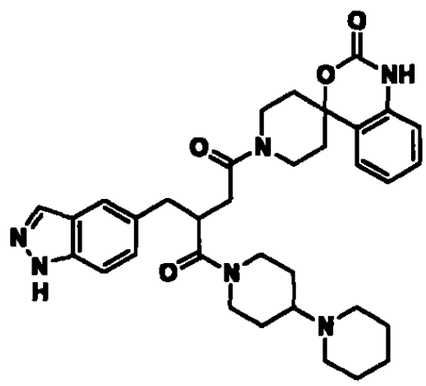
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-1-piperidin-1-yl-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.82 (1H, m),7.37 (1H, m), 7.14 (1H, m), 7.04 - 6.90 (3H, m), 6.73 (1H, d, J = 8.0 Hz), 4.69 (1H, m), 4.56 (1H, m), 4.24 (2H, d, J = 7.2 Hz), 4.02 (1H, m), 3.65 (2H, m), 3.33 (3H, m), 3.07 (3H, m), 2.78 (1H, m), 2.55 (3H, s), 2.36 (1H, m), 1.80 - 1.50 (4H, m), 1.43 (4H, b), 1.26 (2H, b), 0.81 (2H, b). Mass spec.: 543.40 $(MH)^+$.

Example 79

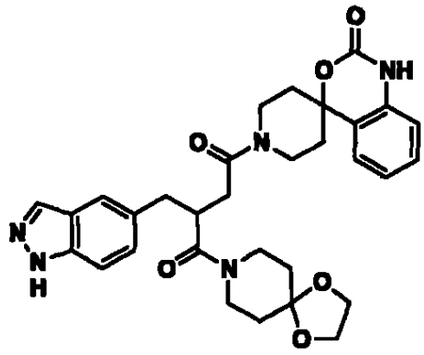
(±)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indazol-5-ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (1H, m), 7.98 (1H, s), 7.54 - 6.85 (7H, m), 4.73 - 4.48 (3H, m), 3.96 - .80 (3H, m), 3.73 - 3.58 (3H, m), 3.17 - 2.78 (5H, m), 2.55 - 2.24 (5H, m), 2.02 - 1.79 (6H, m), 1.70 - 0.79 (7H, m). Mass spec.: 599.31 $(M+Na)^+$.

Example 80

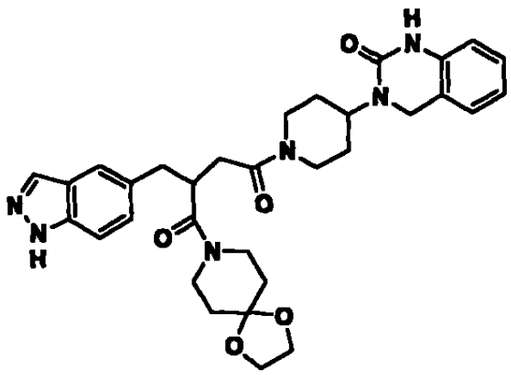
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(1H-indazol-5- ylmethyl)-4-[1',2'-dihydro-2'-oxospiro-[4H-3',1-benzoxazine-4,4'-piperidinyl]-butane-1,4-dione



LC/MS: t_R=1.25 min, 574.25 $(MH)^+$.

Example 81

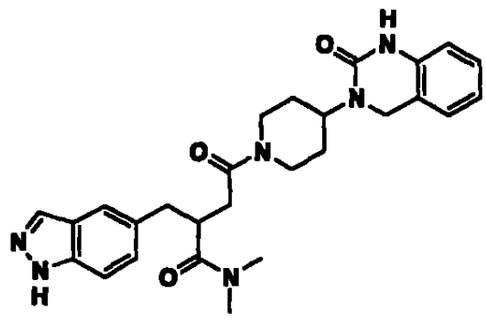
(±)-1-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-2-(1H-indazol-5-ylmethyl)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R=1.34 min, 587.38 $(MH)^+$.

Example 82

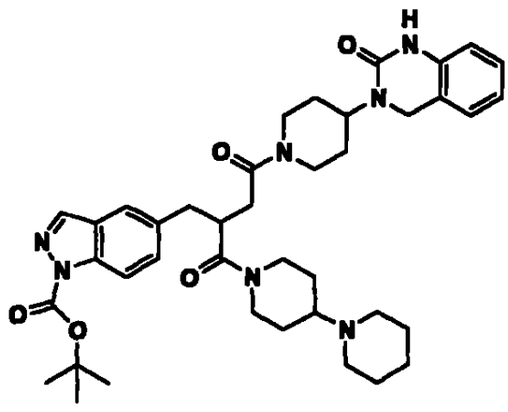
(±)-2-(1H-Indazol-5-ylmethyl)-N,N-dimethyl-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyramide



LC/MS: t_R=1.28 min, 489.33 $(MH)^+$.

Example 83

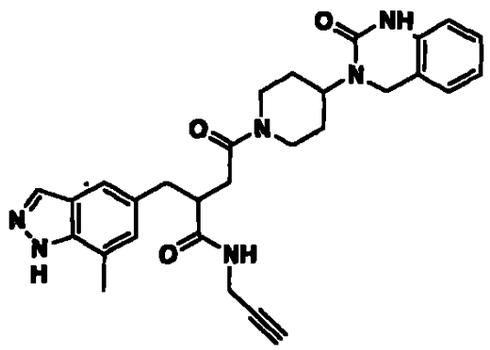
(±)-5-{2-([1,4']Bipiperidinyl-1'-carbonyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyl}-indazole-1-carboxylic acid *tert*-butyl ester



LC/MS: t_R=1.47 min, 742.55 $(M+Na)^+$.

Example 84

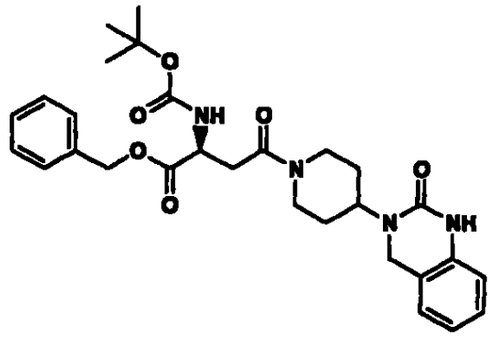
(±)-2-(7-Methyl-1H-indazol-5-ylmethyl)-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-N-prop-2-ynyl-butyramide



LC/MS: t_R=1.33 min, 535.32 $(M+Na)^+$.

Aspartate Intermediates and Examples

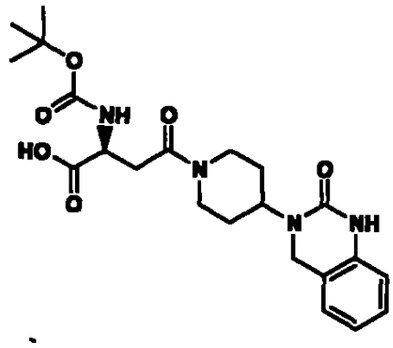
(L)-2-*tert*-Butoxycarbonylamino-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid benzyl ester



To a stirred solution of *N-tert*-butyloxycarbonyl-*L*-aspartic acid-alpha-benzyl ester (1.4 g, 4.33 mmol) and 3,4-dihydro-3-(4-piperidinyl-2(1H)-quinazolinone (1.26 g, 4.33 mmol) in methylene chloride (12 mL) was added 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 1.425 g, 4.76 mmol) in one portion followed by dropwise addition of triethylamine (0.724 mL, 5.20 mmol). The resulting suspension gradually became homogeneous with stirring and was stirred at room temperature overnight (15 h). The mixture was diluted with methylene chloride and

washed with sodium hydroxide (0.5 N) and water. The layers were separated and the organic layer was dried with sodium sulfate, and concentrated *in vacuo* to give a light yellow foam. The crude product was purified by flash column chromatography (10% methanol in methylene chloride) to give a colorless oil. Mass spec.: 559 $(M+Na)^+$.

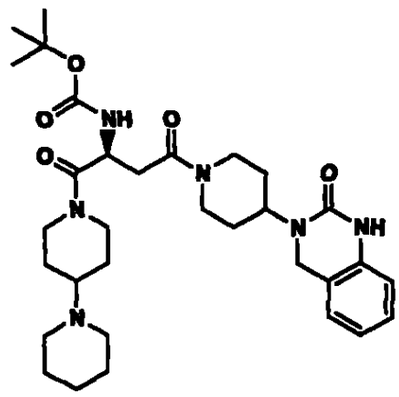
(L)-2-*tert*-Butoxycarbonylamino-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid



To a solution of 2-*tert*-butoxycarbonylamino-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid benzyl ester (1.48 g, 2.76 mmol) in ethyl acetate/methanol (16 mL, 1:1) in a Parr bottle was added 10% palladized charcoal (150 mg) in one portion. Hydrogenation was carried out with a Parr apparatus at 52 psi for 1 h. TLC (10% methanol in methylene chloride) indicated a quantitative conversion. The mixture was filtered and concentrated *in vacuo* to afford a glassy colorless solid (1.14 g, 93%).

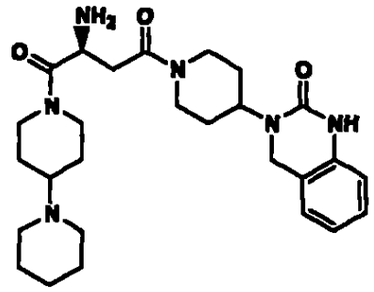
Example 85

(L)-{1-([1,4']Bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-carbamic acid *tert*-butyl ester



To a stirred solution of 2-*tert*-butoxycarbonylamino-4-oxo-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butyric acid (1.14 g, 2.55 mmol) and 4-piperidinyl-piperidine (525 mg, 2.81 mmol) in methylene chloride (20 mL) was added 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3*H*)-one (DEPBT, 840 mg, 2.81 mmol) in one portion followed by dropwise addition of triethylamine (0.427 mL, 3.06 mmol). The resulted mixture was stirred at room temperature overnight (15 h). The mixture was diluted with methylene chloride and washed with sodium hydroxide (0.5 N) solution and water. The layers were separated and the organic layer was dried with sodium sulfate and concentrated *in vacuo* to give a light yellow foam. The crude product was purified by flash column chromatography (10% (1M ammonia in methanol) in methylene chloride) to give a colorless foam (1.08 g, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 – 8.55 (1H, br), 7.05 (1H, br), 6.93 (1H, br), 6.82 (1H, br), 6.72 (1H, d, J = 7.6 Hz), 6.10 – 5.68 (1H, br), 5.20 (1H, m), 54.70 – 4.40 (2H, br), 4.20 (2H, br), 4.01 – 3.82 (2H, br.), 3.10 – 2.88 (3H, br), 2.99 (3H, br), 2.53 (6H, br), 1.90 – 1.10 (23H, m). Mass spec.: 597 $(MH)^+$.

(L)-2-Amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione

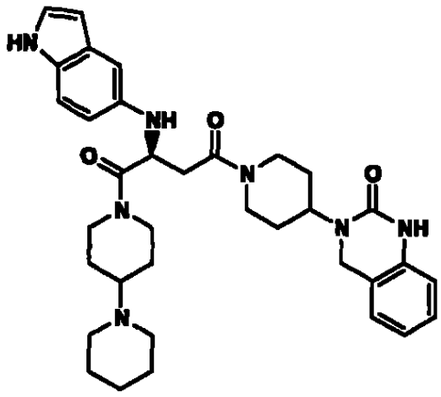


1045
984

To a stirred solution of {1-([1,4']bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-carbamic acid *tert*-butyl ester (1.05 g, 1.76 mmol) in methylene chloride (12 mL) was added trifluroacetic acid (2 mL). The mixture was stirred at room temperature until complete conversion (monitored by LCMS, ca. 15 h). The mixture was then diluted with water and sodium hydroxide (1.5 g) was slowly added with stirring. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give a light yellow foam (860 mg, 98%). Mass spec.: 497 $(MH)^+$.

Example 86

(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(1H-indol-5-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione

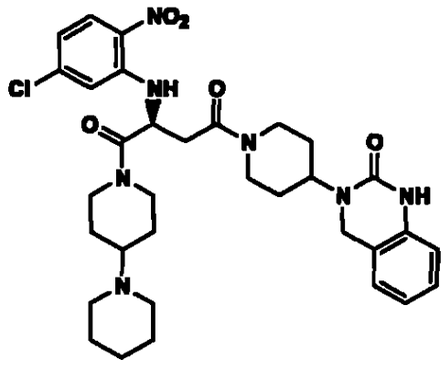


To a solution of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (52 mg, 0.105 mmol) and *N-tert*-BOC-5-bromo-indole (prepared as described in *Tetrahedron* 2000, pp 8473-8482) (31 mg, 0.105 mmol) in tetrahydrofuran (1 mL) in a 5 mL drum vial was added 2-dicyclohexylphosphino-2'-(*N*, *N*-dimethylamino)-biphenyl (4.1 mg, 0.0105 mmol), $Pd_2(dba)_3$ (4.8 mg, 0.005 mmol), and cesium carbonate (54.6 mg, 0.168 mmol) under nitrogen. The vial was sealed with a teflon®-lined cap. The deep orange-colored reaction mixture was heated at 80°C with stirring. The reaction was continued at 80°C overnight. Conversion reached approximately 50% after 17 h. The solvent was removed *in vacuo* and the residue dissolved in methylene chloride and filtered. The desired product was purified by prep arative TLC (10% methanol in methylene

chloride) to afford the *tert*-butyloxycarbonyl-protected product (11 mg, 15%). Mass spec.: 712 $(MH)^+$. This intermediate (11 mg) was dissolved in 3 mL methylene chloride and treated with trifluoroacetic acid (1.5 mL). The colorless solution turned to a tan color and was stirred at room temperature for 1.5 h. The mixture was concentrated *in vacuo* and dried under high vacuum to a give tan powder (15 mg, 100%). Mass spec.: 612 $(MH)^+$.

Example 87

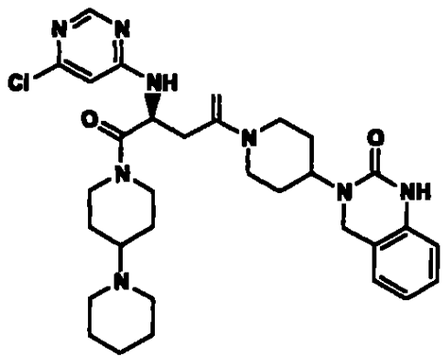
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(5-chloro-2-nitro-phenylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



To a stirred solution of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (33.7 mg, 0.068 mmol) and 4-chloro-1,2-dinitrobenzene (16.8 mg, 0.075 mmol) in ethanol (0.5 mL) was added a saturated sodium bicarbonate solution (4 drops). The mixture was stirred at room temperature for 70 h to approximately 60% conversion. The product was purified by preparative HPLC to give a yellow solid (17.7 mg, 40%). Mass spec.: 652 $(MH)^+$.

Example 88

(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(6-chloro-pyrimidin-4-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione

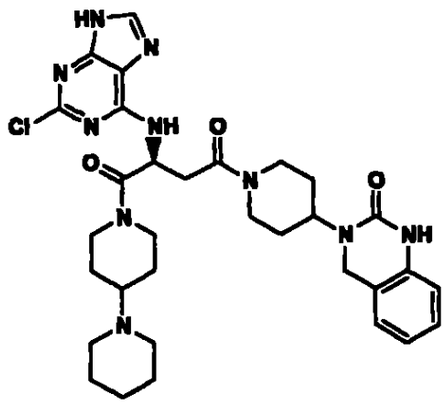


A mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (22.3 mg, 0.045 mmol) and 4, 6-dichloropyrimidine (16 mg, 0.095 mmol) in 2-propanol (0.5 mL) in a microwavable vial was heated at 130°C under microwave irradiation for 40 min. LC/MS indicated 90% conversion. The solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and 1 N sodium hydroxide solution. The organic layer was separated, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography (10 % (1N ammonia in methanol) in methylene chloride) to afford a white solid (23 mg, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, J = 12.8 Hz), 8.04 – 7.81 (1H, 2s), 7.14 (1H, t, J = 7.6 Hz), 7.10 – 6.80 (2H, m), 6.74 (1H, t, J = 8.2 Hz), 6.52 – 6.42 (1H, m), 5.90 – 5.50 (1H, br), 4.85 – 4.40 (3H, m), 4.40 – 4.05 (3H, m), 4.05 – 3.82 (1H, m), 3.20 – 3.00 (2H, m), 3.00 – 2.68 (2H, m), 2.68 – 2.30 (8H, m), 2.05 – 1.90 (2H, m), 1.90 – 0.70 (12H, m). Mass spec.: 609 $(MH)^+$.

Similarly prepared:

Example 89

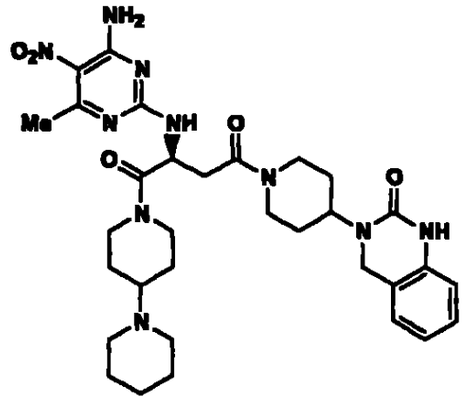
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(2-chloro-9H-purin-6-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R = 1.10 min, 649 $(MH)^+$.

Example 90

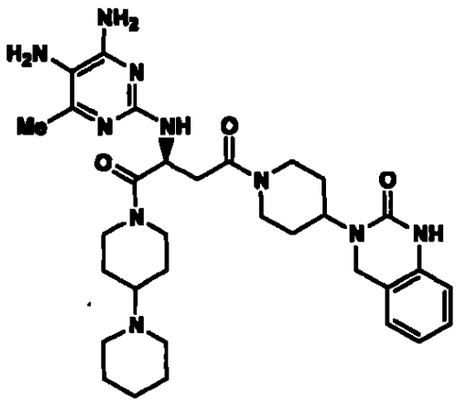
(L)-2-(4-Amino-6-methyl-5-nitro-pyrimidin-2-ylamino)-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R = 1.12 min, 649 $(MH)^+$.

Example 91

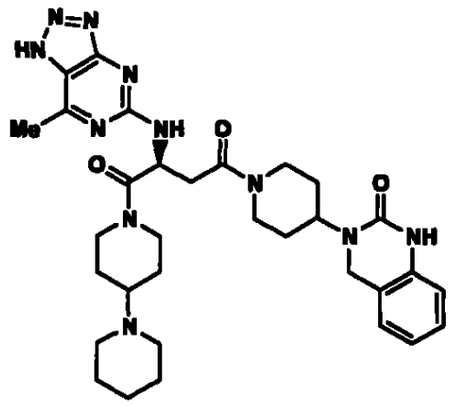
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(4,5-diamino-6-methyl-pyrimidin-2-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



To a solution of 2-(4-amino-6-methyl-5-nitro-pyrimidin-2-ylamino)-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione in 2:1 methanol/ethyl acetate (6 mL) in a Parr bottle was added 10% palladized charcoal (60 mg). The mixture was shaken under a hydrogen atmosphere at 55 psi for 20 h. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to afford a colorless solid (41.2 mg, 49.2% for two steps). LC/MS: t_R = 0.86 min, 619 $(MH)^+$.

Example 92

(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(7-methyl-1H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



To a stirred solution of 1-[1,4']bipiperidinyl-1'-yl-2-(4,5-diamino-6-methyl-pyrimidin-2-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (10.6 mg, 0.0125 mmol) in acetic acid (1.5 mL) was added sodium nitrite (24 mg) followed by a few drops of water. The resulting light yellow solution

1017
939

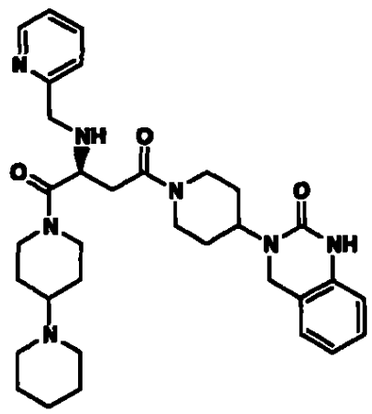
was stirred at room temperature for 6 h. The reaction mixture was diluted with water and methanol and purified by preparative HPLC to afford a colorless oil/solid (3.0 mg, 28%) . LC/MS: t_R = 1.07 min, 630 $(MH)^+$.

General procedure for the synthesis of Examples 93-95:

A mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (0.014 mmol), one of a series of aldehydes (0.07 mmol, 5 equiv) and solid anhydrous magnesium sulfate (0.031 mmol, 2.2 equiv) in 1,2-dichloroethane (3.0 mL) was treated with a catalytic amount of acetic acid and was shaken overnight. Sodium cyanoborohydride (0.07 mmol, 5 eq) was then added in one portion and the suspension was again shaken overnight. Purification was carried out either by filtration through an SCX cartridge or by preparative HPLC.

Example 93

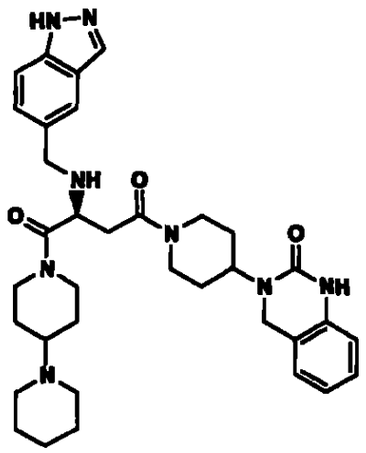
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((2'-pyridyl)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R = 0.87 min, 588 $(MH)^+$.

Example 94

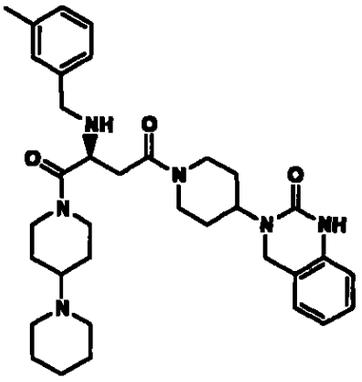
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((5'-indazolyl)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R = 0.92 min, 626 $(MH)^+$.

Example 95

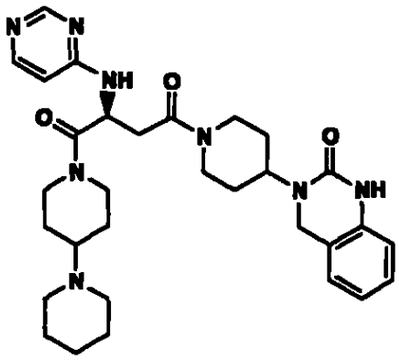
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-((3'-methyl-phenyll)-methyl-amino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



LC/MS: t_R = 1.08 min, 600 $(MH)^+$.

Example 96

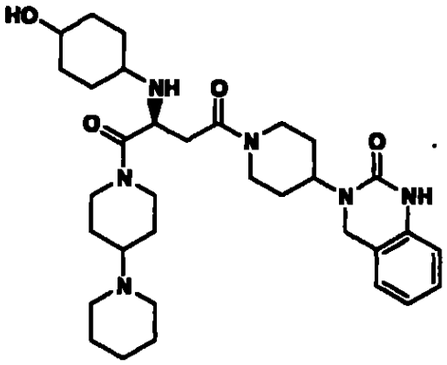
(L)-1-[1,4']Bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-2-(pyrimidin-4-ylamino)-butane-1,4-dione



To a solution of 1-[1,4']bipiperidinyl-1'-yl-2-(6-chloro-pyrimidin-4-ylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (21 mg) was dissolved in 4 mL ethyl acetate/methanol (1:1) in a Parr bottle was added 10% palladized charcoal (10 mg). Hydrogenation was carried out on a Parr apparatus at 55 psi overnight. The degassed mixture was then filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to afford a yellow solid (12.4 mg, 45%). Mass spec.: 575 $(MH)^+$.

Example 97

(L)-1-[1,4']Bipiperidinyl-1'-yl-2-(4-hydroxy-cyclohexylamino)-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione

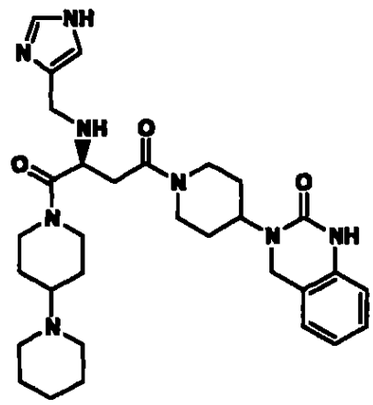


To a stirred mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (47.9 mg, 0.096 mmol) and 4-hydroxy-cyclohexanone (Synthesis reported in *Can. J. Chem.* 1994, *72*, 1699 – 1704) (11 mg, 0.096 mmol) in methanol (1.0 mL) was added excess zinc chloride followed by sodium cyanoborohydride (5 equiv). The suspension was stirred at room temperature for 6 days. The methanol was removed *in vacuo* and the residue partitioned between methylene chloride and 1 N sodium hydroxide. The

aqueous layer was extracted with methylene chloride (3x). The combined methylene chloride solution was passed through a celite cartridge and concentrated *in vacuo*. The residue was purified by preparative TLC (10% (1N ammonia in methanol) in methylene chloride) to afford the desired product as a white solid (15.3 mg, 27%). Mass spec.: 595 $(MH)^+$.

Example 98

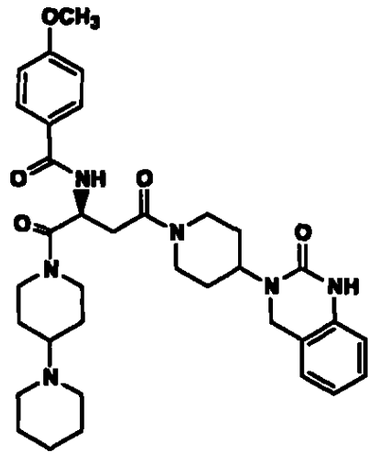
(L)-1-[1,4']Bipiperidinyl-1'-yl-2-[(1H-imidazol-4-ylmethyl)-amino]-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione



To a stirred solution of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (20.6 mg, 0.0415 mmol) and 4-imidazlecarboxyaldehyde (4 mg, 0.0415 mmol) in methylene chloride (1.0 mL) was added sodium cyanoborohydride (8.8 mg, 0.0415 mmol) in one portion. The suspension was stirred at room temperature for 2 days and then partitioned between methylene chloride and 1N sodium hydroxide. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by preparative TLC (10% (1N ammonia in methanol) in methylene chloride) to afford the desired product as a colorless oil that solidified upon standing (6.1 mg, 26%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, J = 4.8 Hz), 7.16 (1H, t, J = 7.6 Hz), 7.10 – 6.85 (3H, m), 6.67 (1H, d, J = 8.0 Hz), 4.85 – 4.63 (2H, m), 4.63 – 4.40 (1H, m), 4.40 – 3.65 (7H, m), 3.25 – 2.40 (10H, m), 2.15 – 0.70 (18H, m). Mass spec.: 577 $(MH)^+$.

Example 99

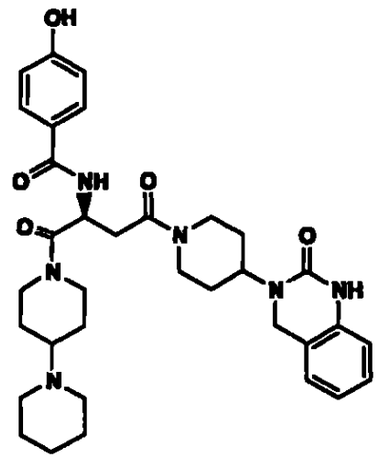
(L)-N-{1-([1,4']Bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-4-methoxy-benzamide



To a stirred mixture of 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (91.5 mg, 0.184 mmol) and *p*-anisoyl chloride (34.6 mg, 0.203 mmol) in methylene chloride was added two drops of triethylamine (35 μL). The light yellow solution was stirred at room temperature for 2.5 h to achieve complete conversion. The reaction mixture was washed with sodium hydroxide (1N) and the aqueous layer was then extracted with methylene chloride. The combined organic layers were passed through a celite cartridge and concentrated *in vacuo* to give a glassy solid. The crude product was purified by flash column chromatography (10% (1N ammonia in methanol) in methylene chloride) to give a glassy solid (92.8 mg, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.47 (1H, d), 8.10 – 7.78 (3H, m), 7.09 (1H, t, J = 7.4 Hz), 6.96 – 6.74 (4H, m), 5.62 – 5.44 (1H, br), 4.75 – 4.40 (3H, m), 4.40 – 4.05 (3H, m), 4.05 – 3.82 (1H, br), 3.76 (3H, s), 3.18 – 2.88 (3H, m), 2.88 – 2.70 (1H, m), 2.70 – 2.30 (8H, m), 2.05 – 1.19 (14H, m). Mass spec.: 631 $(MH)^+$.

Example 100

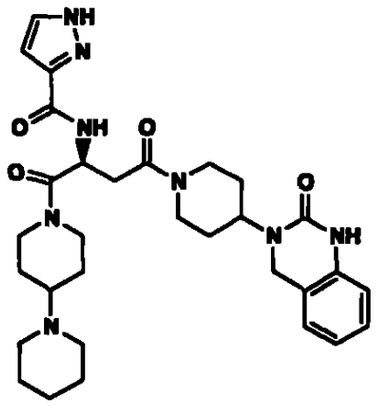
(L)-N-{1-([1,4']Bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-4-hydroxy-benzamide



A stirred solution of *N*-{1-([1,4']bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-4-methoxy-benzamide solution in methylene chloride (69 mg) was treated with boron tribromide (1M in methylene chloride, 0.6 mL), dropwise at room temperature. The resulting suspension was stirred at room temperature for 7 h and then the reaction was quenched with excess triethylamine followed by methanol. The solvents were removed *in vacuo* and the residue was dissolved in methanol and purified by preparative HPLC. LC/MS: t_R = 1.03 min, 617 $(MH)^+$.

Example 101

(L)-1H-Pyrazole-3-carboxylic acid {1-([1,4']bipiperidinyl-1'-carbonyl)-3-oxo-3-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-propyl}-amide

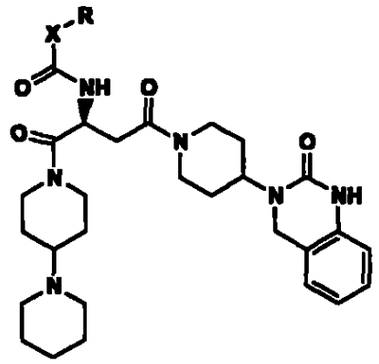


To a stirred solution of pyrrazole-3-carboxylic acid (4 mg, 0.036 mmol) and 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione (13 mg, 0.026 mmol) in methylene chloride (1 mL)

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9-05

was added 3-(diethoxyphosphoryloxy)-1,2,3-benzotriain-4(3H)-one (DEPBT, 8.6 mg, 0.036 mmol) in one portion followed by one drop of triethylamine. The resulting mixture was stirred at room temperature overnight (15 h). The mixture was then partitioned between sodium hydroxide (0.5 N) and methylene chloride. The layers were separated and the aqueous layer was extracted with methylene chloride (3x). LCMS indicated that the product was remained in the aqueous layer. The product was purified by preparative HPLC to give a yellow oil (17.2 mg, 94%). Mass spec.: 591 $(MH)^+$.

General procedure for the synthesis of Examples 102-134:

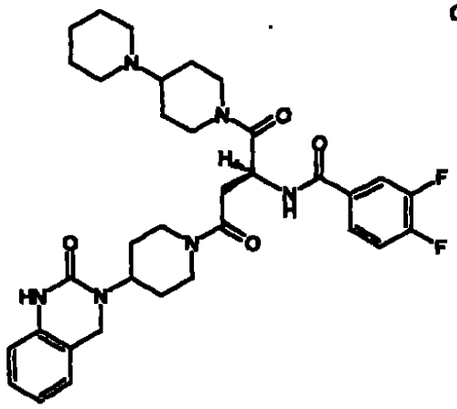
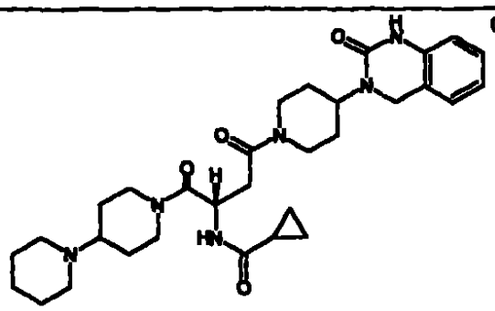
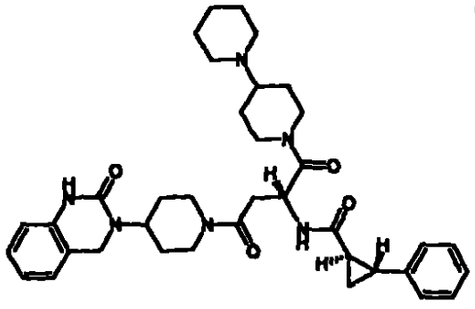
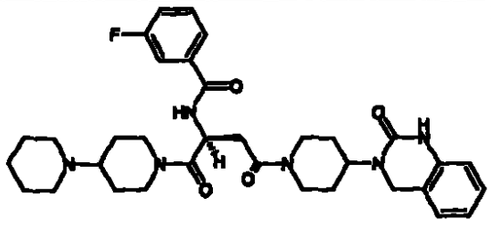


X = C, O

The starting amine, 2-amino-1-[1,4']bipiperidinyl-1'-yl-4-[4-(2-oxo-1,4-dihydro-2H-quinazolin-3-yl)-piperidin-1-yl]-butane-1,4-dione, was dispersed in a 96-well mini-reactor (ca. 10 mg each) in 1 mL dichloroethane. Individual acyl chlorides (ca. 2 equiv.) were added followed by a resin-bound solid-phase piperidine base (4 equiv). The block was shaken overnight. Approximately 4 equivalents of tris-amine resin was added to each well and the mini-reactor was shaken for another 5 h. The reaction mixtures were filtered, and purified by either preparative HPLC or filtration through an SCX cartridge or both. HPLC retention times and mass spectral data for each example are listed in Table 2.

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Table 2. Amides and Carbamates

Example	Structure	HPLC t_R (min)	MS (M+)
102	 Chiral	1.84	637.38
103	 Chiral	1.39	565.45
104	 Chiral	1.89	641.46
105	 Chiral	1.73	619.42

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
BRISTOL MYERS SQUIBB COMPANY

REFERENCIA	Radicación No.	6 53380
	Solicitud internacional	PCT/US2003/038799
	Fecha inicio fase nacional	05/07/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	9837

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 01 SET. 2006
adpa11

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Eve: 378 FASENACIONALI
Act 411 PRESENTACION
Folios: 1024

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
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 se 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 se 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 Diseño Industrial.	( )	( )
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firma Responsable: _____

Fecha: _____